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CONTENTS OF PREVIOUS NUMBER

OCTOBER 1942. NUMBER 4

Long Term Prevention of Tooth Decay Among Diabetic Children. Julian D. Boyd, M.D., Iowa City.

Ingestion of Fluoride and Dental Caries: Quantitative Relations Based on Food and Water Requirements of Children One to Twelve Years Old. F. J. McClure, Ph.D., Bethesda, Md.

Pancreatic Function and Disease in Early Life: II. Effect of Secretion on Pancreatic Function of Infants and Children. Charlotte L. Maddock, M.D.; Sidney Farber, M.D., and Harry Shwachman, M.D., Boston.

Effects of Disease on Nutrition: I. Absorption, Storage and Utilization of Vitamin A in the Presence of Disease. Samuel Spector, M.D.; Charles F. McKhann, M.D., and Emily R. Meserve, M.S., Ann Arbor, Mich.

Effect of Adolescence on Basal Metabolism of Normal Children. Robert C. Lewis, Ph.D.; Anna Marie Duval, Ph.D., and Alberta Iliff, Ph.D., Denver.

Case Reports:

Von Gierke's Disease (Glycogen Disease of Hepatomegalic Type). Report of a Case. Lieutenant Wilbur R. Master, Medical Corps, Army of the United States, and Raoul G. Bowman, Ph.D., Providence, R. I.

Bacillus Alcaligenes Bacteremia Complicating Diabetes Mellitus. D. H. Weintraub, M.D., and E. R. Neter, M.D., Buffalo.

Progress in Pediatrics:

Pancreatic Function and Disease in Early Life: III. Methods of Analysing Pancreatic Enzyme Activity. Harry Shwachman, M.D.; Sidney Farber, M.D., and Charlotte L. Maddock, M.D., Boston.

Abstracts from Current Literature.

Society Transactions:

Chicago Pediatric Society and Chicago Heart Association.

Book Reviews.

News and Comment.

American Journal of Diseases of Children

VOLUME 66 NOVEMBER 1943 NUMBER 5

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LATE EFFECTS OF LEAD POISONING ON MENTAL DEVELOPMENT

RANDOLPH K. BYERS, M.D.
AND
ELIZABETH E. LORD, PH.D.
BOSTON

FOREWORD

The sudden tragic death of Dr. Lord on Jan. 10, 1943 occurred before the completion of the final draft of this paper. It was she who first felt that the minor deviations found on psychologic examination of these children with lead poisoning might be of important significance for the future. It was she who maintained the file of cases, studying them from the psychologic point of view, without encouragement from any one for the first several years.

That lead poisoning occurring in early life usually has a disastrous effect on mental development has not been generally recognized, though the subject of lead poisoning in children has been discussed by many observers. The manifestations of acute involvement of the nervous system have been adequately described, and the gross destructive lesions in the brain consequent to acute lead encephalopathy accompanied by cerebral edema and high intracranial pressure have been recognized. On the other hand, McKhann,[1] for instance, stated: "The neurologic manifestations of lead poisoning usually subside without serious consequences if the ingestion of lead is stopped and the removal of lead from the circulation and its deposition in inert form in the bones can be hastened, as described, by the use of a diet high in calcium together with the administration of cod liver oil or viosterol to accelerate the laying down of new bone."

This point of view, which is pretty generally accepted, fails to take into account the effect of lead poisoning on the growth and development of the infantile nervous system. The present observations, in our opinion, demonstrate that this process may be seriously impaired, showing as they do that of 20 children with mild lead poisoning in infancy, only 1 has progressed satisfactorily in school.

The primary requisite for supporting such a contention is the proof of early lead poisoning. Aub, Minot, Fairhall and Reznikoff[2] in 1925 published a monograph on lead poisoning and in it outlined standards for establishing the diagnosis based on earlier suggestions of Newman, McConnell, Spencer and Phillips. While criticisms of such an outline were undoubtedly valid, it may serve as a concrete basis for discussion. Of first importance was the recognition of a source of ingestion or inhalation of lead. In addition, at least two symptoms from the following list were required: marked pallor or anemia, colic or obstinate constipation, muscular incoordination, peripheral motor paralysis of the most used muscles

Mrs. Penfield Roberts gave valuable assistance in summarizing Dr. Lord's notes on some of the psychologic examinations.

Dr. Lord's work on this paper was done under a grant by the Earhart Foundation, and Dr. Byers' work, under a grant by the Commonwealth Fund.

1. McKhann, C. F.: Lead Poisoning in Children: Cerebral Manifestations, Arch. Neurol. & Psychiat. **27**:294 (Feb.) 1932.

2. Aub, J. C.; Fairhall, L. T.; Minot, A. S., and Reznikoff, P.: Medicine **4**:1, 1925.

(usually the dorsiflexors of the feet in children), basophilic stippling of the red cells, a lead line on the gums and lead in abnormal quantities in the stools and urine. If two of the foregoing symptoms were lacking, a presumption of lead poisoning could be established by the presence of three of a longer list of less specific symptoms, among which were emaciation, loss of appetite, especially for breakfast, vomiting on eating solid food, abdominal pain, loss of strength, headache, insomnia, mental lethargy, tremor, dizziness, encephalopathy, hypertension and articular pains.

Since these suggestions were made, some new criteria for diagnosis have been developed. Vogt,[3] Park, Jackson and Kajdi,[4] Caffey[5] and Kraft and Kato,[6] independently and more or less simultaneously, published papers showing that in

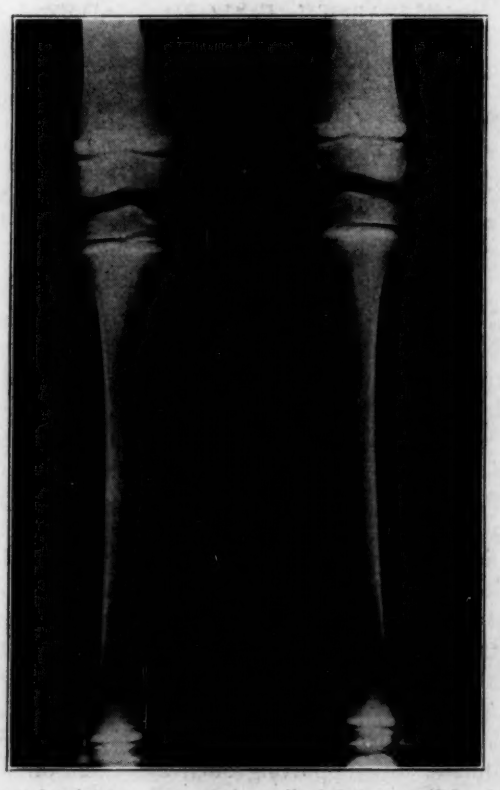

Fig. 1 (case 6).—Well marked deposits of lead at the diaphysial margins of a long bone.

children during the period of rapid growth while the process of lead ingestion was occurring lead was deposited in special concentration in abnormally dense bone at the growing ends of the shafts of the long bones and along the growing margins of the flat bones. These deposits formed a radio-opaque band, comparable in density to that of the lead numerals used to mark roentgenograms, and when well developed were very characteristic. When less well developed they could be simulated by the changes of rapidly healing rickets, by deposits of bismuth salts or possibly of other metals and, finally, by the dense bands resulting from the admin-

3. Vogt, C.: Radiology **22**:87, 1934.

4. Park, E. A.; Jackson, D., and Kajdi, L.: Shadows Produced by Lead in X-Ray Pictures of Growing Skeleton, Am. J. Dis. Child. **41**:485 (March) 1931.

5. Caffey, J.: Radiology **17**:957, 1931.

6. Kraft, E., and Kato, K.: Fortschr. a. d. Geb. d. Röntgenstrahlen **46**:249, 1932.

istration of elementary phosphorus in cod liver oil. Typical dense bands at the growing margins of the shafts of the long bones, in conjunction with a history of ingestion of lead, were considered by the various authors as reliably diagnostic of lead. Much of the roentgen evidence in the present series was seen and interpreted by Dr. Vogt.

Another roentgen sign rather nonspecific was the finding of flocculi of radio-opaque material in the intestinal tracts of children who had recently been chewing paint. It had been of clinical value mainly in calling to the attention of parents previously unobserved pica. It was, of course, much more useful in outpatient

Fig. 2 (case 12).—Recurrent deposits of lead at the margins of the shafts of the long bones.

or office practice than in the hospital ward, where such evidence disappeared in a few days.

In relation to diagnosis, it was also clear from the review of Aub and his co-workers [2] that lead in large amount may be retained in the body, especially in the skeleton, in the absence of any of the clinical evidence of lead poisoning. Although this lead had been regarded as harmlessly stored in the skeleton, they showed that in animals free of symptoms of lead poisoning and protected for months from ingestion of lead small amounts of lead were excreted both by bowel and by kidney for a long time. Since practically all the lead in the bodies of human beings and of animals that had been exposed to lead and then protected from it for a considerable time was in the skeleton, such excretion presupposed

continual solution and transportation by the blood stream of small amounts of lead from the stores in the bones. The same authors also measured the urinary and fecal excretion of lead by patients recovered from lead poisoning and found it virtually uninterrupted for long periods. The skeletons of persons exposed to lead were found to contain from approximately 200 to approximately 900 mg. of lead, and the rate of combined excretion through bowel and kidney of the recovered patients varied between 0.07 and 0.89 mg. daily. Under these circumstances, it would take the person with the least lead about seven months to excrete at the most rapid rate all the lead stored in the skeleton. Since the person with the least lead was an infant who had chewed the paint from her crib "for only a few weeks," it seems likely that the amounts of lead involved in our cases were of the same order of magnitude. It must also be remembered that in a person with such recent exposure to lead, considerable amounts of lead were contained in organs

Fig. 3 (case 6).—Radio-opaque material in the intestinal tract, consistent in its appearance with that of flecks of paint.

other than the bones. In addition, the rate of excretion in our patients was probably in the neighborhood of the slowest rates of excretion, approximately 0.1 mg. daily, for Aub showed that treatment with cod liver oil and a high calcium diet (used more or less faithfully for all our patients) reduced the rate of excretion to such levels.

It seems probable that the disappearance of the lead line from the bones of growing children is not to be taken as an evidence of complete excretion of lead. It seems more likely that processes of reabsorption and redeposition tend to distribute the lead more evenly in the bone and thus destroy the roentgenologic evidence. For instance, 1 child (case 11) four years after the cessation of pica no longer had a lead line in her bones by roentgen examination but still showed stippled cells in her blood and new neurologic signs of damage to her nervous system. Another child (case 17) three years after her acute episode of lead

poisoning no longer had roentgen evidence of lead in her bones but in connection with a bout of vomiting again showed stippled cells.

Indeed, Aub and his collaborators [2] in discussing the storage of lead in the bones, where they felt it to be relatively harmless, stated: "This desirable situation may not be permanent, for slight changes toward either the alkaline or acid side of the usual hydrogen ion concentration of the organism can readily reduce the stability of the tertiary phosphate." Thus, under chemical shifts common in childhood concentrations of lead known to be significant may be recurrently liberated into the circulation.

It is evident, therefore, that the criteria permitting a diagnosis of lead poisoning are ephemeral in relation to the total process of ingestion of lead and its subsequent excretion from the organism. They depend on the presence in the body fluids or tissues of a certain concentration of lead, and the question of whether the conditions to be discussed are due to the continual circulation of subclinical concentrations of lead derived from the stores in the bones, or to the increase in solubility suggested by Aub [2] or to injury sustained by the developing nervous system at the time of acute episodes must remain a matter of speculation for the present. Possibly all three factors contribute.

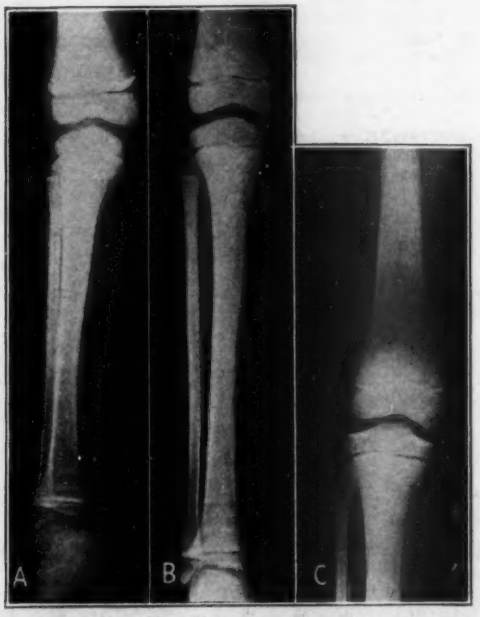

Fig. 4 (case 11).—*A*, at 5 years of age, showing dense bands at the growing ends of the shafts of the long bones; *B*, at 7 years, showing nearly complete disappearance of the roentgen evidence of lead in the long bones; *C*, at 11 years, showing no roentgen evidence of lead in the long bones. At the time roentgenogram *C* was made, the patient's blood showed anemia and stippled cells and she seemed to have a mild encephalopathy.

It is also to be noted that in most instances by the time the difficulties here presented became evident, the diagnosis of lead poisoning, unless established earlier, could no longer be made with certainty by methods now in use. A recent publication by Fairhall and Keenan,[7] describing a relatively simple method for the quantitative determination of lead in urine, may render possible the diagnosis of lead poisoning during the long period of excretion of stored lead after the symp-

7. Fairhall, L., and Keenan, R. G.: J. Am. Chem. Soc. **63**:3076, 1941.

toms and signs of the more acute phases of poisoning have subsided. The usefulness of this method has not yet been proved by wide application.

During the past several years, a number of children who were admitted to the hospital on account of lead poisoning have been repeatedly examined psychologically

Summary Data for 20

Case No.	Age on Admission, Yr.	Source of Lead	Duration of Exposure, Mo.	Pallor	Anemia	Constipation	Peripheral Paralysis	Stippling of Red Cells	Lead Line on Gums	Roentgen Line on Bones	Emaciation	Anorexia	Vomiting	Abdominal Pain	Loss of Strength	Headache	Irritability
1	2 4/12	Chewing paint	..	+	+	..	..	..	..	+	..	+	..	..	..	..	..
2	1 6/12	.....	..	+	+	..	..	+	..	+	..	..	+	..	..	..	..
3	1 6/12	Chewing paint off crib and window sills	12 to 18	+	+	..	..	..	..	+	..	..	..	+	..	..	..
4	2 6/12	Chewing paint off crib, window sills and furniture	20	..	..	..	..	..	..	±	..	+	+	+	..	?	..
5	1 5/12	Chewing paint off crib	..	..	+	..	..	+	..	±	..	..	+	..	+	..	..
6	6 9/12	Chewing paint off crib and furniture	About 5½ yr.	+	+	..	..	+	+	+	..	..	+	+	..	..	..
7	10/12	Chewing paint off crib	Weeks	..	..	..	..	..	..	+	..	+	..	..	..	..	+
8	1 7/12	Chewing paint off crib and window sills	4	..	..	..	..	..	..	+	+	+	..	..	+	..	..
9	3 1/12	Chewing paint off crib and window sills	18	+	+	..	..	..	..	±	..	..	..	..	..	..	+
10	2 6/12	Chewing paint off crib, window sills and furniture	18	..	..	+	+	+	..	+	..	..	..	..	+	..	..
11	2 5/12	Chewing paint off wooden furniture	..	+	+	..	+	+	..	+	+	+	+	+	..	..	..
12	4	Pica (articles not remembered)	..	+	+	..	+	+	..	+	+	+	+	+	+	+	..
13	1 6/12	Chewing paint off crib and window sills	10	..	+	..	..	+	..	+	..	+	+	..	..	..	..
14	11/12	Chewing paint off repainted crib and porch railing	16	..	..	..	..	+	..	+	+	..	..	+	+	..	+
15	3 4/12	Chewing paint	24	+	+	+	..	..	..	+	+	..	..	..	..	..	..
16	4 7/12	Chewing paint off window sills and furniture	24	+	+	+	..	..	..	±	..	+	..	..	..	..	..
17	1 11/12	Chewing paint	..	..	..	..	..	+	..	±	..	..	+	..	..	..	..
18	10/12	Lead nipple shields used by nursing mother	10	+	+	..	+	+	..	+	..	..	+	+	..	..	..
19	2	Lead water pipes; played with paint	..	+	+	..	+	..	..	+	..	+	..	..	..	..	..
20	3	Chewed paint off crib and window sills	48	+	+	..	..	+	+	+	+	..	+	+	+	+	+

by one of us (E. E. L.) and certain deviations noted. In order to make a systematic study of the matter, the records of the Children's Hospital for the past ten years have been reviewed and 128 cases discovered. The yearly rate of admission has tended to decline from 21 in 1931 to 3 in 1939; such cycles may, however, tend to occur in relation to the interest of the staff in the subject. During

the past year medical records of 71 children (38 boys and 33 girls) living near enough to Boston to be available have been reviewed. Of this group, 12 (9 boys and 3 girls) showed gross evidence of cerebral damage at the time of discharge from the hospital and were not further considered. Of the remaining 59 children

Cases of Lead Poisoning

Encephalopathy	Spinal Fluid	Age at Latest Examination, Yr.	I. Q.	Present Status
.....	.....	9	87	Still reading in a primer; sensorimotor defect
.....	.....	9 3/12	67	Repeated first grade; now doing poor work in second grade
.....	.....	8	82	Unreliable, impulsive behavior prevents friendship; unable to learn in school; cannot write name in spite of two years in first grade; sensorimotor defect
.....	.....	6 6/12	94	Cruel, unreliable, impulsive behavior; runaway; unable to get on with other children or adults; excluded from school because of behavior
.....	.....	6 10/12	100	Not progressing in reading or writing; sensorimotor defects
.....	Total protein, 36 mg.	6 9/12 12 6/12	100 82	A nervous person, doing passing work in seventh grade; no significant variation in sensorimotor sphere
.....	.....	9	103	Serious behavior problem; unable to do school work; referred to remedial class; short attention span; special sensorimotor tests not given
.....	.....	6 10/12	96	After a year in first grade cannot write his name, though he is considered smart; sensorimotor defects
.....	.....	6 4/12	87	After a year in first grade has not learned to write or print his name or recognize any figure; sensorimotor defect
.....	.....	9	105	Lively knee jerks, ankle clonus on left; restless and inattentive at school; is having a hard time; beginning fourth grade; mild sensorimotor defect
.....	Normal	10 9/12 15	92	Babinski sign on right; repeated two grades; had emotional difficulties which were helped by tolerance; difficulties in sensorimotor sphere
.....	Normal	10 6/12	75	Repeating fourth grade; to be put into special class
Choked disks	Total protein, 124 mg.	6	90	Expelled from school for setting fires; sensorimotor defect
Hyperactive knee jerks	Normal	6 1/12	109	Behavior unpredictable and impulsive; unable to learn first grade subjects; death at 6 years and 2 months from agranulocytosis after use of sulfanilamide
Confusion; chorea; tremor	Total protein, 63 mg.; 18 white blood cells	7 7/12	91	Convulsions recurrent at long intervals; unable to learn to read; sensorimotor defect
Convulsions at 4 to 4½ years	.....	7 9/12 12 4/12	90 69	Irregular mental development with extreme unpredictability in results of school work and mental tests; scattered convulsions; enlarged ventricles
Two convulsions in few days before admission	.....	6	94	Convulsions recurrent after 5 years of age; after one year in first grade unable to write name or make figures; irregular mental development; mild sensorimotor defect
Bulging fontanel; edema of optic disks	Total protein, 160 mg.; xanthochromia	7	103	Doing well in school; reads and writes normally for age; sensorimotor tests average for age
Tendon reflexes hyperactive	.....	12	Mental tests not given	Repeated first grade; private teacher at home for one year; then second grade; repeating grades so that he will start fifth grade next fall; enuresis
Hyperactive reflexes; bilateral Babinski sign	Total protein, 108 mg.; white blood cells	9 6/12	79	General intelligence level between 7 and 8 years; doing badly in third grade

discharged as cured, many have received repeated examination by the psychologist, and of these, 20 have now entered the school system. These 20 form the basis of the present report.

A tabular review of the 20 cases is presented in the table. In all but case 2 an adequate source of the lead ingested was disclosed by the history, for this child

lead poisoning was considered an unimportant subsidiary diagnosis in relation to the acute mastoiditis for which he entered the hospital. In 18 cases the lead was obtained by chewing paint off cribs, window sills or furniture. In many instances the parents stated that they had repainted the crib, a practice which would vitiate the use of lead-free paint by the most conscientious of furniture manufacturers. The frequency with which children chewed window sills and painted furniture points to the importance of preventing the use of lead-containing paint on any and all interior finish, on porch railings and on other objects which are in reach of children's teeth. In 1 instance ingestion of lead appeared to be the result of the use of lead nipple shields by a nursing mother.

From the diagnostic point of view there seemed ample evidence to accept these children as having had lead poisoning. All but 1 generously fulfilled the diagnostic criteria outlined in Aub's article, and, in addition, all had roentgen evidence either consistent with (designated by ± in the table) or characteristic of lead poisoning (designated by + in the table). The 1 child who did not have conclusive evidence of lead poisoning was a girl of 10 months who was admitted to the hospital because of anorexia and failure to gain weight satisfactorily since birth. Her diet had been irregularly unsatisfactory throughout her life. Soon after she cut two teeth (all she had at the time of admission), she began to gnaw the paint off her crib. Two days before admission she became irritable. On admission she was a small, irritable baby, continually whining and scratching her palms, soles and genitals. Except for a few beats of clonus at her left ankle, her physical examination was not remarkable. Cytologic examination of her blood showed no pathologic changes, but roentgenograms of her long bones showed dense metallic shadows at the ends of the shafts of the long bones, considered diagnostic of lead. Treatment by protection from ingestion of paint and use of an adequate diet for her age supplemented with dibasic sodium phosphate and cod liver oil was supervised for two months in the outpatient department. The itching of the palms and soles continued. While it may be argued that actual poisoning by lead had not occurred at this time, it was clear that she had ingested paint and stored a heavy metal in her bones in the pattern characteristic for lead.

With respect to the nervous system the cases fell into three groups. In the first group, 9 cases, there was no evidence suggesting involvement of the nervous system. In the second group, 3 cases, there was peripheral neuritis but no clinical sign of cerebral involvement, and in the last group, 8 cases, there was more or less conclusive evidence of encephalopathy. The symptoms and signs among the latter were choked disks, bulging fontanels, hyperactive tendon reflexes, convulsions, confusion, choreiform movements and changes in the spinal fluid. In no case were these symptoms severe, and in every instance they appeared to have cleared completely at the time of the patient's release from the hospital ward. The presence or absence of evidence of involvement of the nervous system bore no relation to the eventual intellectual development of the children; indeed, the only truly successful member of the group had the most severe encephalopathy encountered among the 20 children.

Considering the early age at which the ingestion of lead began, it was difficult to forecast what the intellectual development of any of the children would have been. When the 20 patients were considered as a group, its motor development, as obtained by history, fell in the normal range. Since most of the individuals began to be exposed to lead during middle infancy, other developmental criteria were not applicable. Detailed developmental histories were not available in all instances, but 8 of the children were reported to have sat alone at an average age of 6.9 months, 14 to have walked at an average age of 14.3 months and 11 to have

been using words at an average age of 18 months. These developmental items applied to 15 of the children; 2 more were 10 months old when admitted to the hospital and must have been active to have obtained their lead; for another child the statement of normal development was not documented; for the nineteenth no developmental data were given, and the twentieth child was first seen when she was 6 years old because of failure to do school work as well as had been expected by her family. It was the opinion of the medical staff that these were "normal children" at the time they were originally seen in the hospital. It was obvious that 1 or 2 unsatisfactory children might be found in any group of "normal children" picked in this way at such an early age, but, on the whole, the expectation of reasonable average progress in school was justifiable for the group. The developmental data also disposed of the suggestion that these infants exhibited pica because of mental defect.

After recovery from their lead poisoning these 20 children made an extremely poor record in competition with their fellows. Their difficulties were in relation to both the intellectual and the emotional spheres. The intellectual difficulties were capable of rather exact analysis, and, since in part the emotional difficulties were dependent on them, they will be discussed first.

With one definite and a second possible exception, none of the 20 children succeeded in school. The causes of their failures were probably manifold. For the group as a whole, at about the time of entrance to school the intellectual ratings averaged 90, with a spread from 67 to 109. The usual correlation between the intelligence quotient and the ability to learn in school did not hold for the group, the second most successful child having an intelligence quotient of 82 while several with quotients above average were unable to do school work. For the 5 children with intelligence quotients ranging from 67 to 85 slow progress in school seemed well enough explained by the low intelligence level. These children did not show the mental irregularities to be discussed in relation to the children with better intelligence levels, since special defects merged into the general intellectual inadequacy.

Throughout the psychologic examination of the children with good intelligence levels and poor scholastic attainment, sensorimotor defects were found in most instances. This is not the place to discuss the tests used to show such defect, since they must be varied to suit the age of the child examined, since they must be given by an experienced psychologist trained in their use, and since they have been well described in the literature of psychology. In brief, however, in the earlier age groups sensorimotor defect was shown by inability to manipulate blocks, to fit forms into holes in a form board and to perform similar acts. In the preschool years inability to copy simple figures, such as crosses, triangles and squares, proved to be important. In the school ages inability to reproduce by memory the designs of the Ellis Visual Designs Test [8] or of the Pintner-Cunningham Test No. 7,[9] to deal with the block designs of the Wechsler-Bellvue Test [10] or to build up the associations to pictures necessary for success in the Wood Picture Completion Test [11] were found. All of these tests are designed to bring out a subject's ability

8. (*a*) Bronner, A., and others: A Manual of Individual Mental Tests and Testing, Boston, Little, Brown & Company, 1927. (*b*) Wood, L., and Shulman, E.: J. Educ. Psychol. **31**:591, 1940.

9. Pintner, R., and Cunningham, B. V.: Primary Mental Test, New York, World Book Co., 1922.

10. Wechsler, D.: The Measurement of Adult Intelligence, Baltimore, Williams & Wilkins Company, 1939.

11. Wood, L.: J. Genet. Psychol. **56**:383, 1940.

to deal with shape, direction, space and projected imagery, all matters of the utmost importance in a child's success or failure in the fundamental school of technics. In the grades, inability to learn to write or read or deal with numbers in arithmetic was the result of such defect, even though verbal ability might be good. By contrast, many of the children showed normal or even superior abilities in the language field, and on this account several of the most severely handicapped children made relatively high scores on the Stanford-Binet tests. Such children were frequently socially responsive, especially in their preschool years, and were considered "bright" by parents and teachers, the latter often stating that the children could do better if only they would try.

One child, as previously intimated, appeared to have recovered completely; at 7 years his intelligence quotient was 103 and he was progressing satisfactorily in school. At 25 months, however, he presented intellectual difficulties of a sort that were permanent in other children of the group. He was an attractive, good-natured boy, socially responsive, pleasant, imitative and amenable. His understanding of language allowed him to carry out simple commands in the test situations appropriate for a 21 month old child. He associated the proper pictures with Mother Goose Rhymes, and he liked to listen to verses. In the use of language he was more like an 18 month baby in that he had a vocabulary of only half a dozen words and did not combine words. From the point of view of adaptive behavior, he pushed single blocks imitatively but made no effort to aline them. He piled large blocks at home but could not make the necessary adjustments to pile small cubes, being less adequate than most 18 month old babies in this respect. He adapted the circle to the form board, but though he placed the other forms over their holes he could not make the adjustments necessary to insert them, again dealing with shape and spatial orientation like an 18 month baby. With a crayon he scribbled and made strokes as do most babies of 21 months. In summary, he was imitative and resourceful, but the sensorimotor element in the adjustment of blocks and the fitting of forms into a board was definitely not as advanced as his understanding of language and his social response. As he grew older, these sensorimotor disabilities diminished, and at 7 years he appeared to be intact. His ability as a baby to scribble imitatively with a crayon was not found in any of the other children of the group who were examined early. He was the only child in the entire group who did well in school.

One other child in the group kept up with her class in school with great difficulty. She was a pleasant, docile person, recognized as relatively incompetent by her family. Her intelligence quotient at 7 years was 102, but at 12 years it was only 82. Sensorimotor capacity as shown by the Ellis Memory Test was below the twenty-fifth percentile for her age, and her ability to organize her visual impressions as measured by the Wood Picture Completion Test was in the second decile for her age. Thus her difficulties were most obvious in the sensorimotor sphere, but they were not far out of line as compared with her general intellectual level.

Eleven children were examined when they were between 18 months and 2½ years of age. Each of the 11 exhibited more advanced reactions to language tests than to the tests of sensorimotor control. Seven were using words as well as one would expect for their age, whereas in 4 speech was delayed, but the play with blocks and forms was consistently less adequate than speech. In all but the child already discussed as completely recovered a definite lag in the ability to make imitative adjustments with the crayon was found.

Six children were examined between the ages of 4 and 5 years. They answered comprehension questions well; some counted, and some even named colors. In

each instance there was more than the average difficulty in adjusting blocks in picture puzzles and in reproducing drawings. Two of the children, approaching 5 years, had begun to be interested in making letters, but their copy of letters was disoriented and they were unaware of the displacement. One particularly attractive little girl aged 4 2/12 years made an extremely favorable impression in the ward. She was so friendly and cooperative with the doctors that one of them said, "I should like to adopt that child." On the Stanford-Binet scale she had a mental age of 4 8/12 years and an intelligence quotient of 112. The comprehension questions were answered adequately not only on the Stanford test but on several other tests. Although she matched outline shapes, showing adequate visual perception, she had more difficulty in fitting the blocks in the Seguin form board than most 3 year old children. She had more than average difficulty in block building, and her hand was unsteady as she traced the Porteus Cross. Although her ideation was good in the drawing of a man and she made a figure with head, eyes, legs and arms, the whole figure was disoriented. Here again are found good ideation, verbalization and social response for a 4 year old child but less competence than that of the average 3 year old child in the adjustment of forms.

These deficits in the younger children did not in themselves seem more than minor deviations; but when children who still exhibited them encountered the school system, severe difficulties in learning became evident. Two of the children have been promoted each year, to the fourth and seventh grades at 9 and 12 years respectively, but complaints of inattention, restlessness and inaccurate work continue to be made about them. Of the children in the first grade, the comment has been made that they "seem smart enough but do not learn." Another child is "bright but restless and does not concentrate, is learning a few words with help from his mother at home but is having a terrible time with writing." A mother reported: "He is smart, and I have no complaints. Although the youngest boy in his group, he is going to make his first communion with the others." When this situation was explored a little more fully, it was found by the psychologist that though he was 6½ years old and had an intelligence rating of 96, at the end of the first year in school he did not recognize a single word and had not learned to write his name. He could make numbers, but they were disorientated. In general, these comments reflect the frustration of parents and teachers with these responsive, verbally able children who because of sensorimotor defect could not learn the technic taught in the first grades in school. The table summarizes the school situation in regard to all 20 children, and their clinical histories appended afford more detail.

In addition to difficulties in the general intellectual and sensorimotor spheres, other evidences of interference with the normal development of the nervous system were found scattered through the series. For a few children successive psychologic examinations showed significant drops in the intelligence quotient. These drops were felt to be the result of failure of mental development rather than of actual mental deterioration. As a result, though the chronologic age advanced, mental growth did not keep up with it. Cases 4 and 11 are examples. In case 16 the fall in intelligence quotient was associated with recurrent convulsions and such great variability in intellectual function from day to day that it seemed likely that mental deterioration had actually occurred.

Recurrent convulsions appeared in 3 of the children, at 4, 4½ and 5½ years of age. Of these, 1 (case 16) showed enlarged ventricles on pneumoencephalographic examination at 12 years of age. One girl who had peripheral neuritis as a baby acquired a positive Babinski sign, first noted when she was 11 years old, and 1 boy, who was discharged from the hospital as well at about 3

years of age, had hyperactive reflexes and sustained clonus at the left ankle when reexamined at 9 years.

Behavior difficulties were common throughout the series. Much of this behavior could be classified as "forced reaction to stimuli in the environment" described by Strauss and Werner [12] as an evidence of cortical damage. It was apparently the result of loss of the normal inhibitory function, thought to reside in the cortex. It was usually described as unreliable impulsive behavior, cruel impulsive behavior, short attention span and the like. It made several of the children friendless and difficult at home and in school. Three were excluded from school on the basis of behavior, 1 for setting fires in the school, another for repeatedly getting up and dancing on the desks and other furniture and the third for sticking a fork into another child's face.

In some children the untoward behavior seemed to occur under any and all circumstances. An example is a boy (case 14) who first came to our attention at 23 months because of irritability. His lead poisoning was diagnosed and treated, and he was sent home as cured. From that time on, he presented a severe behavior problem, with crying, irritability, refusal to eat, soiling, wetting and abdominal pain. His mother, a good-natured, kindly, humorous woman who handled him with admirable tolerance and insight, was given many brisk talks by the medical staff on how children should be brought up. From time to time he was admitted to the hospital in an attempt to modify his behavior or because of a suspicion of appendicitis. In the wards, his behavior, though not as flagrant as at home, continued essentially unchanged. It was felt that his improvement in the wards was due largely to the fact that a routine requiring much of one person's time could be established for him and in addition to the fact that the nurses and doctors caring for him had no deep emotional attachment to him. Fundamentally he remained irritable, impulsive and distractable, and it was impossible for teachers to deal satisfactorily with him in the group situations in the kindergarten and the first grade.

On the other hand, some of the children acquired behavior difficulties motivated in part, at least, by the frustration resulting from the impact of scholastic disciplines on their intellectual deficits. An example is a girl (case 11) who was first thoroughly studied at 5 years of age because of peripheral neuritis due to lead; at that time no psychologic difficulties were suspected. At 11 years of age she returned to the hospital because of difficulty with school work and emotional disturbances. She was sullen, withdrawn and insecure and on medical examination was found to have positive Babinski signs (a new observation) and stippled cells in her blood. Psychometric examination showed sensorimotor defects, and with the assistance of an extremely intelligent school supervisor, allowances for her disabilities were made and treatment for lead poisoning instituted. The behavior difficulties smoothed out at once, and when last seen, at 15 11/12 years, she was a pleasant, attractive-looking girl, with a quiet and poised manner, getting along fairly well in the eighth grade but unable to do arithmetic. She had repeated two grades, and her family were hoping mildly that she might reach high school. She had made real gains in the specific sensorimotor field, her score of the Ellis Memory Test being normal for her age and her performance with the Wechsler-Bellevue Block Designs and the Wood Picture Completion Test more nearly up to expectation for her age than before. These findings suggested that her psychologic state at the time of her depression was due, in part at least, to a reactivation of her latent lead poisoning.

12. Strauss, A. A., and Werner, H.: Am. J. Psychiat. **97**:1194, 1941.

The conditions imposed by present day culture on children with good intelligence quotients and sensorimotor defects are very difficult. Their excellent verbal capacity and social responsiveness make it seem impossible to parents and teachers that they could not learn if only they would. A good example is presented in case 15. At 8 years the patient was a pretty, outgoing child, large for her age, with an intelligence quotient of 91 and no ability to learn to read or write because of sensorimotor defect. The choices before those responsible for her school planning were three. The first was to keep her back in the first grade, where her large size and advanced age combined with her inability to compete in learning would certainly humiliate her. The second possibility was to put her into the second grade, where the defective preparation and learning defects would be certain to frustrate her. The last possibility was to let her go nominally into the second grade but to protect her from competition with the other children by giving her tutoring in the academic subjects. Such a plan could be worked out only in a tolerant and well staffed public school system.

Lead poisoning in these 20 children began in infancy. In order to obtain the lead, all but 1 must have developed at an average rate from the motor point of view. None of them exhibited evidence of severe acute encephalopathy, yet only 1 lived up to the promise of his early development. In some, such failure was parallel to a generalized defect in mental development, resulting in a readily recognizable lowering of the intelligence quotient. In others, though the intelligence quotient remained well within normal limits, a specific failure of development in the sensorimotor sphere was the outstanding finding.

That failure of intellectual development is somehow connected with improper development of the cerebral cortex is well accepted. Sensorimotor defect has been studied by several observers. Goldstein and Scheerer [13] found it especially in relation to abstract designs, as an evidence of cortical disease or injury. Wechsler [10] found that failure in his block design tests correlated well with organic cerebral lesions, and Lord and Wood [14] have shown that failure in the sensorimotor sphere was common in a group of children with known cerebral disease and uncommon in a group of children under treatment for psychiatric disturbances.

There is ample evidence that the cortex of an infant is not as yet completely active functionally. From the motor standpoint, Kennard [15] showed that decortication of infant monkeys produced little disability as compared with decortication of adults, and Byers [16] showed that hemiplegia in early infancy produced a distinctly different clinical picture from that found after the upright posture had been attained. The normal processes of intellectual growth and development are thought to be due to processes of maturation taking place in the cortex. It seems likely, therefore, that the lead in the circulation of an infant in some way interferes with the changes normally occurring in the cortex and in a high percentage of cases prevents the normal growth and development of the cortex.

SUMMARY

A follow-up study of 20 school children who had been hospitalized in infancy or early childhood because of lead poisoning has been presented. None of them

13. Goldstein, K., and Scheerer, M.: Abstract and Concrete Behavior, Evanston, Ill., American Psychological Association, Inc., 1941, vol. 53, no. 2, p. 131.
14. Lord, E. E., and Wood, L.: Am. J. Orthopsychiat. **12**:414, 1942.
15. Kennard, M. A.: Relation of Age to Motor Impairment in Man and in Subhuman Primates, Arch. Neurol. & Psychiat. **44**:377 (Aug.) 1940.
16. Byers, R. K.: Evolution of Hemiplegias in Infancy, Am. J. Dis. Child. **61**:915 (May) 1941.

exhibited striking evidence of encephalopathy during their primary admission, and all were adjudged to have made a complete recovery from lead poisoning when discharged from the original hospitalization.

The length of the cycle of ingestion, storage and elimination of lead in relation to the relatively short duration of the symptoms and signs allowing a diagnosis of lead poisoning is emphasized. It seems probable that lead poisoning of the sort here discussed can at present be recognized in only a small percentage of cases.

Failure of the normal processes of growth and development of the cortex prevented all but 1 of the 20 children from progressing satisfactorily in school.

Lead poisoning is a serious disease developing from entirely man-made hazards, which should be controlled by appropriate legislation.

REPORT OF CASES

CASE 1.—A boy of 2 years 4 months was admitted to the outpatient department because of lack of appetite. He was the only child of healthy parents. He sat at 7 months and walked at 14 months but was talking only a little at the time of his first visit. He had chewed the paint "off everything" when he was smaller, though at just what age and for how long was not stated. He was completely out of control of his parents at the time of his admission, screaming for what he wanted, refusing to give up his bottle and exhibiting impulsive and irritable behavior. He had been "pale for a long time."

Physical examination showed the boy to be small and pale but otherwise revealed nothing remarkable. A blood smear showed moderate achromia but no stippled cells. His urine was normal. Roentgenograms of his long bones showed dense bands of metallic deposit at the growing ends of the shafts, characteristic of lead poisoning. Twenty drops of halibut liver oil and a high milk diet were prescribed, and later iron and ammonium citrates was added.

After visiting the hospital he continued to chew the paint off the window sills and furniture at home, but finally this habit stopped spontaneously. At 4 years he was still small but had become shy and repressed. Psychologic appraisal showed poor speech and considerable difficulty in handling test materials, suggesting a general mental level below average, with mental irregularity due to specialized difficulties.

At about this time his mother died of pneumonia and he was boarded out. Treatment with vitamin D in various forms and dicalcium phosphate was, however, carried on. He continued to be rather unsatisfactory physically, intellectually and emotionally.

At 9 8/12 years he was in the third grade in school, though he had failed to learn to read. At home he was difficult and impulsive. A psychologic appraisal indicated an intelligence quotient of 87, with special disabilities in the sensorimotor sphere. His score on the Wood picture completion test was at the third decile for his age, and on the Ellis visual design test it was worse than any calibrated score.

CASE 2.—A boy of 1½ years was admitted to the hospital because of projectile vomiting of ten days' duration. He was born normally at full term and did well as a baby. His dentition was late, beginning at 14 months, and he began to walk and talk just prior to his entry to the hospital. Two months before his admission scarlet fever and running ears developed, one of which continued to discharge to the time of admission. Two weeks before entry he began to vomit projectilely at night, and he continued to do so to the time of admission.

Physical examination showed a pale child with a discharging right ear. Roentgenograms showed a clouded and eroded right mastoid and a broad band of metallic deposit at the growing end of the long bones, characteristic of lead poisoning. A roentgenogram of the abdomen showed much dense flocculent material, probably paint, in the intestinal tract. His blood showed a secondary anemia (hemoglobin content 55 per cent and 4,100,000 red cells), many stippled cells on smear and an elevated percentage of polymorphonuclear leukocytes.

A mastoidectomy was performed on the right side, and treatment with calcium gluconate, dibasic sodium phosphate and viosterol in oil [17] was carried out. He did well and was discharged after three weeks in the hospital. At this time psychologic appraisal showed that he handled materials like a 15 month old baby, with no special defects.

At 9 2/12 years psychologic appraisal showed an intelligence quotient of 67, with no specialized defects. In school he was in the second grade, having repeated the first grade.

17. The preparation used in this and succeeding cases contained 10,000 U. S. P. units of vitamin D per gram.

CASE 3.—A boy of 18 months was admitted to the outpatient department because of irritability and crying at night as if in pain. His development was normal. He sat up at 7 months, walked at 13 months and was using words at 18 months. When about 1 year of age, he began to chew the paint off his crib and had continued to do so. In spite of this, he was sent home as presenting a behavior problem.

Eight months later he reappeared with the same complaints and vomiting. His crib had been covered with cloth, but he had taken to chewing the paint off window sills. Roentgenograms of his long bones showed a narrow band of metallic deposit at the growing ends of the long bones, but in spite of letters to his parents he did not report for treatment for six more weeks. At this time his hemoglobin content was 40 to 50 per cent and a blood smear showed no stippled cells. Cod liver oil (½ ounce [15 cc.] daily) and dibasic sodium phosphate were prescribed, and a further warning about ingestion of lead was given to the parents. A month later roentgenograms showed much more pronounced metallic deposits at the growing ends of the shafts of the long bones.

A few weeks later vomiting recurred once or twice daily, and the boy became irritable. Though he had been prevented from chewing paint, it was discovered at this time that the pipes in his home were leaden. He still had a secondary anemia (hemoglobin content 59 per cent and 4,500,000 red blood cells), but on several examinations no stippled cells were found. At this admission, when he was 2½ years old, he was seen by the psychologist, who found his development below the standards for the 2 years, in contrast to his chronologic age. He was discharged from the hospital; treatment with disodium phosphate, viosterol in oil and phenobarbital was continued at home, and the health department was asked to do what was necessary to free the drinking water from lead.

At 8 years and 4 months he had difficulty in getting on with other children because of his unreliable, impulsive behavior. He had not acquired his first grade technics, in spite of two years of instruction, and was not able to write his name. Psychologic appraisal indicated a mental age of 6 11/12 years and an intelligence quotient of 82.

CASE 4.—A girl of 2½ years was admitted to the hospital because of temper tantrums and abdominal pain occurring during the nine months prior to admission. Her development had been average. She sat at 6 months, stood at 8 months and talked at 15 months. From the time she was 9 months old she exhibited marked pica, and until the time of admission she continued to chew paint from her crib, the furniture and window sills. At about 20 months she began to have attacks of screaming and banging her head, which lasted fifteen to ninety minutes, made her blue and tremulous and left her exhausted. During the two weeks before her admission she had complained of abdominal pain and vomited projectilely several times. Although she began to use single words at 15 months, she was using only single, rather unintelligible words at the time of admission.

Results of the physical examination and laboratory investigation were not remarkable. Roentgenograms of the long bones showed dense bands along the diaphysial margins, consistent with lead poisoning.

In the hospital she fell out of bed and was taken home on this account by the parents. Four years later, at the age of 6½ years, she returned, having been excluded from school because she danced on the furniture in the classroom and because of similar uncontrollable behavior. In addition, she was cruel to animals, bit people for the pleasure of seeing them bleed and ran away by hopping street cars. In the interim her father and mother had separated several times and divorce proceedings had been instituted. She was unable to get on with other children because she always insisted on having her own way. A large variety of punishments had failed to control her.

Physical and laboratory investigation showed nothing unusual.

Psychologic investigation showed an intelligence quotient of 95 (Terman L), but a marked lack of mental control. She could not apply herself to any problem for more than a very short period, and she was unable to learn in school situations, even with individual instruction. Her auditory memory span was extremely short. She could repeat only three digits correctly. She could not learn a two line nursery rhyme. She could not learn the names of the individual letters comprising her name, though she could print her name. She was excluded from school because she danced about on the desks and piano.

CASE 5.—A boy of 17 months was admitted to the hospital because of diarrhea and vomiting of three days' duration. He had been born normally and had developed normally, sitting up at 6 months and walking at 13 months. At the time of his admission speech had not developed. He had had frequent bouts of diarrhea and vomiting, usually accompanying infections of the upper respiratory tract, which had begun when he was 2 months old. For some months before admission he was known to be chewing the paint off his crib, which was made of metal.

On admission to the hospital he showed mild dehydration and was drowsy. Except for slight evidences of rickets, the physical examination showed no abnormality. Two days later blood smears showed a few stippled cells. Roentgenograms of his long bones at this time showed a narrow band of increased density at the ends of the diaphyses, consistent with lead poisoning.

He was treated for dehydration and was sent home on an average diet with added viosterol in oil (15 drops), dibasic sodium phosphate (30 grains [0.19 Gm.]) daily and calcium lactate (30 grains [0.19 Gm.]) daily.

He returned a year later with the same complaints, and though he was 2½ years old he had not acquired speech. In spite of his mother's efforts, he had continued to chew paint.

Physical examination showed a screaming, unresponsive child who continued to bang his head about and beat it with his hands for some time after admission. His gait seemed definitely unsteady, but otherwise nothing remarkable was found.

His blood showed a mild secondary anemia, and on spectroscopic examination many times the normal amount of lead was found in the blood. After three weeks of treatment with cod liver oil (2 drachms [7.75 cc.] daily) and a high calcium diet, this level was found to be greatly diminished. Roentgenograms of his long bones still showed heavy bands at the end of the shafts.

His irritability diminished, but psychologic examination showed that he did not use words and suggested sensorimotor disturbances.

A few weeks later he returned with an acute otitis media and a digestive upset, which subsided quickly. At this time his blood serum showed a trace of lead on spectroscopic examination, while the clot showed a good deal more. It was reported that his pica had disappeared.

At 3 years and 8 months he returned, drowsy and dehydrated after several days of projectile vomiting. His fundi were hyperemic, and the optic disks were poorly outlined. Otherwise the results of the examination were unremarkable. A lumbar puncture was not done, but the other usual laboratory procedures indicated no abnormal conditions. Roentgenograms of his bones no longer showed any suggestion of deposits of lead.

At 4 years and 5 months he was readmitted, with pneumonia, from which he recovered without incident. After this he was transferred to the neurologic ward for appraisal. His language development was normal for his age, but he had difficulty in the use of crayons and adjustment of forms and blocks, diagnostic of sensorimotor impairment. He has returned for psychologic check-ups from time to time because has has been unsatisfactory to his teachers. At 6 10/12 years his mental age (Stanford-Binet) was 6 10/12 years and his intelligence quotient was 100, but it was impossible for him to do any of the cube designs which are usually satisfactorily dealt with at 6 years. He was not progressing in reading or writing in school.

CASE 6.—A girl of 6 years and 9 months was admitted to the hospital because of vomiting of six days' duration. Her own past history and that of the family were irrelevant except that she had chewed the paint off her crib and had exhibited other forms of pica from infancy until about six months before admission to the hospital. She had entered school in the first grade eight months before, and disappointment was expressed because of her failure to learn as well as had been expected. There had been one previous bout of vomiting of two days' duration initiated by a blow on the abdomen six months before admission. Abdominal pain and vomiting three or four times in twenty-four hours had begun six days before admission and were tending to become more severe.

Physical examination showed a thin, pale, dehydrated girl with teeth in poor condition and a pronounced lead line on the gums. Her fundi showed no abnormalities, and no abnormalities were found on neurologic examination. Her blood showed a secondary anemia (hemoglobin content of 50 per cent and 2,600,000 red cells), and about 2 per cent of the red cells were stippled. Spectroscopic examination of her blood and spinal fluid showed a large and definitely pathologic amount of lead present. The total protein content of the spinal fluid was 36 mg. per hundred cubic centimeters. Otherwise the fluid was unremarkable. Roentgenograms of the long bones showed some density at the growing ends of the shafts of the long bones insufficiently marked to allow a definite roentgen diagnosis of lead poisoning. A roentgenogram of the abdomen showed much dense flocculent material in the intestines consistent in appearance with flecks of paint.

Treatment with sodium phosphate and milk did not alleviate the vomiting, and because of continuing dehydration and acidosis she was given physiologic solution of sodium chloride subcutaneously and 10 per cent solution of dextrose intravenously. Two hours after this she had a generalized convulsion, which was relieved forty-five minutes after its onset by paraldehyde given rectally. She was then treated with calcium gluconate, milk, sweetened

fruit juices and atropine. She gradually improved and was discharged on the twenty-second hospital day, eating well. At the time of discharge an increase in density of the dense bands at the ends of the shafts of the long bones was noted on roentgen examination.

A psychologic examination given the day before her discharge showed an intelligence quotient of 100 and adequate response to all tests.

Two years later she was seen in the outpatient department because of nervousness and crying in her sleep. Her physical examination and her blood showed no abnormalities, and roentgenograms of her long bones showed faint scars of the previous dense bands in the diaphyses.

At 12½ years she was considered a nervous person by her father, but she was doing passing work in the seventh grade in school. Mental tests revealed an intelligence quotient of 82, with no significant deviations.

CASE 7.—A girl of 10 months was admitted to the hospital because of poor appetite and refusal of food since birth and irritability for two days. She was born normally at full term, and weighed 6 pounds 7 ounces (2,920 Gm.). Since birth she had eaten poorly and gained slowly. Orange juice and cod liver oil had been refused or vomited, apparently quantitively. Since cutting two teeth (time unstated), she had chewed the paint off her crib.

On physical examination she was a small, irritable baby, constantly scratching her palms, soles and genitals. There was ill-sustained ankle clonus on the left, but otherwise results of physical and neurologic examinations were unremarkable. Her blood showed no anemia and no stippling.

Roentgenograms of her long bones, taken because of the suspicion of scurvy, showed a line of increased density at the growing ends of the diaphyses, characteristic of lead poisoning.

She was treated with an average diet, cod liver oil and dibasic sodium phosphate, which she took well, but the scratching of her palms and soles continued in the hospital and for the two months during which she was followed in the outpatient department.

She was seen at long intervals because of infections until she was 6 years old, when the school sent her back to the hospital because she was irritable, nervous and inattentive. At 9 years she returned with the same complaints, to which was added the statement that in spite of an adequate intelligence rating she would not do her school work. She was considered to present a serious behavior problem and had been referred to a remedial reading class. Her attention span was very short. Her intelligence quotient was 103 (Stanford-Binet), but sensorimotor tests were not given.

CASE 8.—A boy of 19 months was first seen at the hospital because of poor appetite and loss of weight. His family history and his past history were not remarkable. At about 14 months he stood up and chewed paint off his crib, and later he chewed it from window sills and other beds.

Although he stood alone at 14 months, he did not walk alone until he was 23 months old, apparently because of loss of strength.

At 2 years and 2 months he was admitted to the hospital because of refusal of food and violent behavior, consisting of tearing up toys, defecating on the breakfast table and the like. Physical and neurologic examinations revealed nothing remarkable. Laboratory examination revealed no abnormalities of the urine, blood or spinal fluid.

Roentgenograms of the long bones showed broad bands of increased density at the ends of the long bones, consistent with lead poisoning.

Psychologic examinations were given at 2⅞12 and 2⅞12 years. On the second examination the following facts were noted: "In the past five months the child shows considerable advance in vocabulary, but there has been little or no advance in his ability to manipulate blocks and forms or to use a crayon imitatively."

At 6⅝12 years he had a mental age of 6⅞12 years (Stanford-Binet) and an intelligence quotient of 96. In spite of this, he had not learned to write his name although he was at the end of the first grade. With four reversals, he made the numbers to ten. He had not learned to read at all. For example, he read "boy, cat, dog, play" as "black, red, gray."

CASE 9.—A boy of 3½12 years was admitted to the outpatient department because of pallor and eating paint and dirt. He was the third child of healthy parents, was born at term by low forceps delivery and seemed vigorous at birth. He cut his first teeth at 6 months, walked alone at 14 months and was using words purposefully at 16 months. From the time he stood up, at 10 or 11 months, he chewed the paint off his crib and window sills. He was irritable and cranky.

On physical examination he was pale and difficult to manage. His blood showed a hemoglobin content of 55 per cent; his urine contained a slight trace of albumin, and roentgenograms of his knees showed dense bands at the growing margins of the bones, characteristic of lead

poisoning. He was put on a high calcium diet with added iron and viosterol, and warning about further ingestion of lead was given his parents. With this treatment his family reported that he became much less irritable. His hemoglobin content reached 85 per cent in two months, and he was dismissed as well.

At 6½ years of age he returned in response to a follow-up letter. After a year in first grade he had not learned to write or print his name, to recognize any words or to make figures. He was less adequate with picture puzzles and in copying designs than most 5 year old children, while his verbal capacity was relatively adequate. By the Stanford-Binet standards he had a mental age of 5½ years and an intelligence quotient of 87.

CASE 10.—A boy of 2½ years was admitted to the hospital because of fever and difficulty in walking of a few days' duration. His father, aged 21 years, had suffered for nine years from attacks of syncope. His mother and one younger brother were well. He was born normally and did well as a breast-fed infant. He walked at 1 year, began to talk at about 2 years and was talking well at the time of admission. He had had a few acute infections of the respiratory tract but had otherwise been well. From the time he learned to stand, he had chewed the paint off his crib, window sills and furniture, a habit which had never been controlled. He had always been constipated. Three days before his admission to the hospital a fever developed, and two days before admission he became weak and dragged his legs in walking.

Physical examination showed a rather uncooperative child, whose left knee jerk and both ankle jerks were absent and who showed bilateral foot drop. His blood showed a hemoglobin content of 85 per cent and a red cell count of 5,000,000, but on smear 0.7 per cent of the red cells were stippled. His urine and spinal fluid were normal. Roentgenograms of his legs showed bands of moderately increased density at the growing ends of the diaphyses suggestive of lead poisoning. He remained in the hospital twenty-four days and was treated with daily doses of calcium lactate (30 grains [0.19 Gm.]) and viosterol in oil (10 drops). The weakness cleared up gradually, more quickly on the right side than on the left, and on the twenty-fourth day he was discharged in good condition, having gained 3 pounds (1,307 Gm.). His parents were instructed to guard against further ingestion of lead and to continue the use of viosterol and a high calcium diet.

He was seen irregularly in the orthopedic department during the following year for care of the pronation of his feet. Two years later incisions were made in his ears because of acute otitis, without incident.

At 7½ years he was brought to the hospital because of nervousness. The father and mother had separated, and the children were in the care of their grandmother. The boy was in the third grade and was reported to be doing well. The mother was told to improve her discipline.

At 8 10/12 years he returned with the same complaints. His knee jerks were lively, and there was clonus at the left ankle. The school reported that he was restless and inattentive, especially in the first two grades.

Psychologic examination (Stanford-Binet) showed a mental age of 9½ years and an intelligence quotient of 105, but his rating on the Ellis memory test was below the twenty-fifth percentile for his age. He was beginning the fourth grade.

CASE 11.—A girl of 2 5/12 years was seen in the outpatient department because of vomiting of several weeks' duration and occasional abdominal pain. Except that her general condition was poor and that she was pale, results of her physical examination were not remarkable. Her blood showed a mild secondary anemia and her urine a moderate amount of pus. Although an appointment was made for a cystoscopic examination, she was not seen again until she was 4¼ years old, when she came with the history that the vomiting and abdominal pain had continued intermittently and that at fourteen months and again at two months before her admission to the hospital she had had fever and pains in her extremities. The account suggested muscular rather than articular pains. When she tried to get up after the pain subsided, she could not walk because of weakness and had marked foot drop. When she was seen after the second attack, her knee jerks were present. No other reflexes are recorded. A history of chewing wood was obtained, and her blood was examined for stippled cells, without success.

A year later, at 5½ years, she was admitted to the hospital with the same complaints. Her history revealed no new facts save that her development had been average. She had held up her head at 5 months and walked at 1 year. The age at which speech developed was not stated. She had never been well and strong since the original attack of pain and weakness at the age of 3 years; though partly recovering, she had relapsed each late summer and fall. At this time her family stated definitely that in chewing wood she had chewed painted articles of furniture.

On this occasion she showed pronounced weakness of all her voluntary muscles, with complete paralysis of her diaphragm, demonstrated by fluoroscopic examination. There was no evidence of intracranial pressure. Her tendon reflexes were abolished except for both biceps jerks, which could be obtained. Sensation seemed unimpaired. Her blood showed 1.8 per cent stippled cells and a mild secondary anemia. Roentgenograms of her long bones showed narrow dense bands at the growing ends of the shafts of all the long bones and, in addition, three less well defined areas of density proximal to these suggesting recurrent lead poisoning. Her spinal fluid was not remarkable.

A definite diagnosis of peripheral neuritis due to lead was made, and an attempt was made for two days to cause excretion of the lead with use of ammonium chloride, but she vomited so severely that this was abandoned and treatment with calcium lactate and cod liver oil started, and she was transferred to the neurologic ward, where she was given massage and exercises in a tank. With this treatment her neuritis cleared slowly, and after three months of treatment her blood still showed 2.3 per cent stippled cells.

Two years later, at 7 years of age, she was seen in the outpatient department in response to a follow-up letter and was thought to be entirely well. Roentgenograms at this time still showed faint bands of density some distance behind the growing ends of the long bones, thought to be due to the old deposits of lead.

Four years later, when she was 11, she was returned to the hospital because of difficulty with school work and emotional disturbances, depressional in character. She had been free of physical symptoms in the meantime. Physical examination showed slight pallor, slight weakness of the right side of the face, lively tendon reflexes and persistently positive Babinski signs on both sides. Her blood showed a secondary anemia (hemoglobin content 50 per cent and red cells 4,000,000) and a few stippled cells. Her urine showed a very slight trace of albumin. Spectroscopic examination of her blood, urine and spinal fluid showed about one hundred times the concentration of lead found in normal persons. In spite of these results, roentgenograms of the long bones showed no evidence of lead deposits. Encephalograms showed no gross evidence of cerebral damage. Treatment for lead poisoning was again instituted, and concessions commensurate with her abilities were arranged.

At 15½ years she was a quiet, well poised girl, getting along happily but slowly in the eighth grade, though totally unable to do arithmetic. The family hoped she might get into high school and possibly finish it, but they were no longer pushing her scholastically.

Repeated psychologic examinations were made. At 5 8/12 years her mental age (Stanford-Binet) was 6 2/12 years and her intelligence quotient 106. The test showed irregularities and inability to copy the square at the 4 year level, and her hand was unsteady as she traced the Porteus cross.

Her poor sensorimotor control was further shown by her inability at 6½ years to copy letters or write her name.

At 10 10/12 years her intelligence quotient was 92 (Stanford-Binet), but in the Stanford reading test her paragraph meaning scored at grade 2.8, her auditory memory was poor, and her sensorimeter capacity as tested by the Ellis Visual Designs test was very poor (score 3).

At 15½ years she came in again. The Stanford-Binet test was not repeated, but the sensorimotor tests were given once more. She had made a real gain in this respect. Her score was average for her age on the Ellis Visual Designs test. She succeeded on three of the five block designs, though they were more than usually difficult for her. On the Wood Picture Completion test her score was 113, which was the third decile for her age.

Case 12.—A 4 year old girl was admitted to the hospital because of anorexia, loss of weight and progressive weakness of eight weeks' duration. She was the fourth child of healthy but divorced parents and did well throughout infancy. She sat up at 6 months, walked at 14 months and talked at 18 months. Pica was noticed by the mother at the beginning of the present illness; the child broke bits of plaster off the wall and ate them. No certain consumption of paint was remembered. Weakness developed rather rapidly over the period of eight weeks so that she could not support her weight or pick up objects.

Examination showed a weak, emaciated little girl with great muscular weakness but no complete paralyses. The diaphragm hardly moved actively at all. All tendon reflexes were absent. There was marked bilateral wrist drop and toe drop. Sensation to a pin and to touch appeared intact. No evidence of intracranial pressure was found.

Laboratory investigation showed a secondary anemia (hemoglobin content 60 per cent and red blood cells 3,200,000) and about 1 stippled cell per high power field on smear. Her spinal fluid was normal. Roentgen examination showed definite bands of metallic deposit at the ends of the shafts of the long bones, considered typical of lead.

The patient remained for two months in the hospital on a high calcium diet with added iron and cod liver oil. Her anemia improved fairly rapidly, but her weakess was still

crippling. She remained in a convalescent home another four months. Two months before her discharge from the home she was walking, and at the time of discharge she was walking well and seemed healthy.

Vomiting and abdominal pain were recurrent during the next four months, and five months later they became severe and were accompanied with return of the peripheral neuritis. She was readmitted to the hospital unable to stand and with respiratory embarrassment severe enough to require the use of a Drinker respirator.

Physical examination and laboratory examination showed conditions similar to those noted previously, except that all were more pronounced. Roentgenograms of her skull showed beginning separation of the coronal sutures. Her diaphragm was completely paralyzed, and the metallic deposits in her long bones were more intense than ever. She was treated with high intake of calcium, large doses of vitamin D and intramuscular injections of magnesium sulfate. Her strength returned gradually, and she was again discharged to a convalescent home three and a half months after admission to the hospital, still unable to walk. No definite source of lead was identified. Psychologic examination at the time of her discharge showed an intelligence quotient of 87 and difficulties in learning not explained by subnormal intelligence alone.

Soon after this admission her mother died of tuberculosis in a sanatorium. The child was placed in a convalescent home, where she remained six months, and was discharged able to walk, with straps to control her toe drop. At this time roentgenograms of her long bones no longer showed lead deposits.

At 10½ years a psychologic appraisal showed an irregular mental examination, with an intelligence quotient of about 75 (Stanford-Binet). She was repeating the fourth grade and looking toward a special class or an industrial class.

CASE 13.—A boy of 18 months was admitted to the hospital because of vomiting of six weeks' duration. He was the only child of healthy parents, was born normally and did well as a baby. He held up his head at 5 months, sat up at 6 months, stood at 10 months and walked alone at 13 months. At 15 months he had a vocabulary of 3 words. He began to chew paint off his crib at 8 months, and as soon as he learned to walk he chewed it off the window sills and furniture. Vomiting had gradually increased in frequency to several times daily, and during the two weeks before admission he had exhibited strabismus and an unsteady gait.

Physical examination showed a somewhat pale baby. His fontanel was closed, and percussion of his head gave a cracked pot sound. Both optic disks were choked, and there was an alternating internal strabismus.

His blood showed a secondary anemia (hemoglobin content 55 per cent and red cells 5,400,000) and many stippled cells on smear. His spinal fluid was under greatly increased pressure and had a total protein content of 124 mg. per hundred cubic centimeters. Roentgenograms of the skull showed separated sutures, and roentgenograms of the long bones showed a dense wide band at the growing ends of the shafts of the long bones, characteristic of lead poisoning.

He was treated with intravenous injections of 20 per cent solution of dextrose and disodium phosphate and percomorph liver oil by mouth, and he was discharged in three days much improved. His family was instructed to protect him from paint and to treat him with a high milk diet and percomorph liver oil at home.

Two months later he returned to the outpatient department in good condition. His eyes were straight, but the fundi were not seen.

At 4 years he returned because of knockknees, and his mother gave a history of his having had two convulsions during the previous six weeks. At that time roentgenograms of his long bones showed some distortion of the ends of the diaphyses, but the heavy bands of lead deposit had disappeared.

He next returned, at 6 years of age, because of behavior difficulties which had been growing more pronounced since he was 2 years old. In kindergarten he had stuck a fork into another boy's face. In first grade he had been expelled for stealing pencils and pens. At home he had set the apartment on fire twice. Psychologic appraisal at 6½ years showed a mental age of 6 years and an intelligence quotient of 92. In spite of this, he could not write his name legibly or recognize any of the simplest words. On a brief visuomotor test he showed very poor visual memory and even reproduced a square as an almost circular figure.

CASE 14.—A boy of 23 months was admitted to the hospital because of irritability of one year's duration. His history, except for pica, was irrelevant; the family history was normal. He sat at 7 months, walked at 15 and talked at 18 months.

At about the time he learned to sit up he began displaying pica, eating several coats of paint off the available portions of his crib, carriage and porch railing. He also had eaten cloth, papers of all sorts, curtains, gloves, matches and pencils, and his own stools and canine stools as well. His appetite for food had suffered tremendously, and he had never eaten well. During the year before his entry into the hospital he had been extremely irritable. During the two months before entry he had become unsteady on his feet, and during the week or two before admission he had had abdominal pain and diarrhea.

Physical examination, including examination of the fundi, showed no abnormality except poor nutrition and hyperactive tendon reflexes. His blood showed no anemia, but there were numerous stippled cells on smear. Roentgenograms of the long bones showed heavy bands of density at the ends of the shafts, diagnostic of lead poisoning. His spinal fluid was not remarkable. Psychologic examination showed poor intellectual development at this time, which, taken with his early developmental history, suggested a slowing up of development.

He was treated with disodium phosphate and viosterol, and his family was instructed to guard against ingestion of lead. At home his irritability continued, as did his pica, but his parents attempted to remove all lead from his environment. He gradually improved in stability, but any infection, such as one on the dorsum of a finger, brought out the old symptoms; however, he steadily improved in language ability.

Nine months later he was again admitted because of irritability, frequent soiling and wetting of himself and a weak gait "like that of a little baby just learning to walk." His blood showed a secondary anemia but no stippling, and roentgenograms of his long bones still showed metallic deposits. An encephalogram indicated normal spinal fluid and normal ventricular outlines. In the ward his behavior improved, but his play was more like that of a 20 to 24 month old child than that of one of 32 months and his concentration and attention were poor.

The moment he returned home his behavior returned to its former low level. Vomiting and abdominal pain appeared in bouts, once severe enough to cause his admission to the hospital under suspicion of appendicitis. At 4½ years he was a problem in kindergarten, and the following year he entered the first grade, where he was having great difficulty in learning to read and write, in spite of an intelligence rating of 109.

At 6⁹/₁₂ years he entered the hospital with a severe tracheobronchitis, for which intubation became necessary, and, in addition, he was treated with sulfanilamide for six days in doses maintaining concentrations of the drug between 10 and 15 mg. per hundred cubic centimeters of blood. Twelve days after the use of sulfanilamide was stopped, an agranulocytosis developed, from which he died in sixteen days.

CASE 15.—A girl of 3¹¹/₁₂ years was admitted to the hospital because of vomiting of three and one half months' duration. Her father had been treated for syphilis for two years. The date of his infection was unknown. Her mother was well, and there were five older siblings who were well. The oldest child had died, and the third pregnancy had resulted in miscarriage. The patient was born normally at term and did well on bottle feeding. She had had irregular amounts of orange juice and cod liver oil through infancy, but since infancy her diet had been adequate. She walked at 1 year and began to talk at the same time. At 10 months she began to exhibit pica, eating paint, bark, linoleum and dirt. Three and a half months before admission to the hospital she began to vomit from one to five or six times a day, to lose her appetite, to be constipated and to have dreams bordering on hallucinations at night. She lost 6½ pounds (2,948 Gm.) during this period.

Physical examination showed a pale, restless child with constant choreiform movements and a mild state of mental confusion. Her tendon reflexes were not obtainable.

Her blood showed a hemoglobin content of 58 per cent and a red cell count of 4,700,000. There were no stippled cells on repeated examination. Her urine was not remarkable. Her spinal fluid contained 18 white cells and 63 mg. of protein per hundred cubic centimeters. Roentgenograms of her long bones showed moderately broad metallic zones at the ends of the long bones, characteristic of lead poisoning. Wassermann and Hinton reactions of the blood and spinal fluid were negative.

She was treated with disodium phosphate and large doses of viosterol daily. Her confusion and vomiting subsided promptly, but in the ward she showed pica which was very difficult to control. She was sent to a convalescent home, where she remained two months. At first she seemed dull for her age, but in a few weeks she became responsive and attractive.

At 3⁷/₁₂ years she reported to the outpatient department. At that time her right hand was so unsteady that she used the left by preference. She played with the test materials on psychologic examination like a 2½ year old child, showing special difficulties in the differentiation of shapes, though her language was adequate for a 3 year old child.

She returned to the hospital at 7⁷/₁₂ years in a generalized convulsion. The mother stated that she had been well and was in the second grade in school but was unable to learn to read.

She had shown no pica since the previous admission to the hospital. The convulsion was controlled with ether and paraldehyde, and the next day, save for bites on her tongue, results of physical examination were unremarkable. Cytologic examination of her spinal fluid and blood yielded unremarkable results. Roentgenograms of her long bones showed some disturbances in growth at the ends of the long bones but no metallic bands. After recovery from the convulsion she used her left hand poorly as compared with the right for fine movement.

Psychologic appraisal revealed an intelligence quotient of 91 (Stanford-Binet). It had been 102 by the same examination a year before, with specialized defects in the field of spatial orientation. She was above the average for her age from the point of view of general information. In school work she proved totally unable to learn to read, although she could copy words readily. On the Wood Picture Completion test her associations were so simple that the results were bizarre and unscorable. She failed in all the cube designs appropriate for 6 year old children. She did picture puzzles less well than the average 6 year old child. On the Pintner-Cunningham Test no. 7 she made a great number of unpredictable errors, perseverating from one design to the next.

CASE 16.—A girl of 4 7/12 years was admitted to the hospital because of convulsions which had first appeared when she was 4 years of age. Her family, birth and past history were not remarkable. She walked at 13 months and used single words at 18 months. She had been known to chew paint, furniture and newspaper since before she was 2 years old. For some time she had had a poor appetite and severe constipation. Isolated convulsions had accompanied high fever at 4, 4 5/12 and 4 7/12 years.

Results of her physical and neurologic examinations were not remarkable. Laboratory studies showed no abnormalities save for mild secondary anemia (hemoglobin content 55 per cent). Roentgenograms of the long bones showed a broad band of increased density at the ends of the long bones, consistent with long-standing lead poisoning. A diagnosis of lead poisoning was made and treatment with vitamin D and a high calcium diet instituted.

Scattered convulsions recurred during the ensuing three years, but from 8 to 10 years of age she was free of them. At 10 years sudden recurrent attacks of gagging and hiccup developed, which were accompanied by confusion lasting a matter of minutes, and from 12 years of age she again had recurrent frank convulsions. Pneumoencephalograms showed symmetric enlargement of the lateral and third ventricles in a cranial vault of average size and were interpreted as indicative of diffuse cerebral atrophy.

Psychologic examinations were made at various ages. At 5 years her intelligence quotient (Stanford-Binet) was 90, with pronounced irregularities, and she exhibited difficulty in learning new material in spite of the adequate rating. At 8 years similar results were obtained. At 12 1/12 years she gave a very poor and irregular performance on the Terman test, her results indicating a mental age of 8 years and an intelligence quotient of 65. She could not deal with the picture absurdities or comprehension at the 7 year level, while she succeeded with two items of comprehension at the 9 year level. On the Wood Picture Completion test she did as well as the average 9 year old.

In dramatic contrast to her low rating she attained fifth grade score in most subjects on the Metropolitan achievement tests. Although her actual test performance was so confused that she characteristically failed more tests than she passed, many of her failures were on the easier tests, while some of her successes were in fractions and decimals.

The school reported that in the sixth grade she was a desirable pupil and worked conscientiously under a slight strain to keep up her grades. Her mental capacity was so unpredictable that it was felt that plans for her education should be formulated more with reference to her teachers' attitudes than to the child's actual ability to keep up.

During the past winter she has been out of school for ten weeks because of appendicitis.

CASE 17.—A girl of 1 11/12 years was admitted to the hospital because of convulsions and a rash. Her mother had observed that she was chewing paint at 1 year and 10 months. One week later, in connection with fever, she had a convulsion which left her exhausted for several days. Her local physician demonstrated stippled cells in her blood at this time and referred her to the hospital, where roentgenograms of the long bones showed dense bands at the end of the diaphyses, consistent with lead poisoning.

After that she remained well as far as her family knew, except that she vomited easily and often. When the vomiting was severe, at 5 years, her local physician again found stippled cells in her blood and treated her successfully with calcium and vitamin D.

At 5 years and 3 months she displayed frequent lapses of consciousness lasting one or two minutes, sometimes accompanied by falling and involuntary voiding and usually followed by sleepiness for some minutes.

Pneumoencephalograms at this time showed normal ventricular outlines. Roentgenograms of the long bones showed no evidence of lead, though stippled cells had been found three months before.

Psychologic examination at 6 years, when she was in the first grade, showed irregularities of intellectual development. On the Stanford-Binet test her intelligence quotient was 94. She had a poor memory for stories, and after nearly a year in school she had not learned to write her name or make figures, though she had learned to read.

CASE 18.—A boy of 10 months was admitted to the hospital because of irritability and vomiting of three days' duration. He was born by forceps delivery, and, because he spit up blood on the first postnatal day, he received one transfusion. He was breast fed up to the time of admission to the hospital, and his mother had used lead nipple shields throughout his life. At 10 months he sat up with assistance. Three days before admission he became irritable, vomited projectilely and complained of abdominal pain. These symptoms continued to the time of admission.

On physical examination he was pale, his fontanel was bulging and there was a slight degree of edema of both optic papillae. His temperature ranged between 102 and 103 F. for two weeks.

Laboratory examination revealed a mild secondary anemia (hemoglobin content 70 per cent and 3,300,000 erythrocytes) and 2 to 5 stippled cells per oil immersion field on smear.

His spinal fluid was xanthochromic, was under increased pressure and showed a total protein content of 160 mg. per hundred cubic centimeters and 12 mononuclear cells per cubic millimeter.

Roentgenograms of the long bones showed dense bands at the end of the diaphyses, and roentgenograms of the skull showed separation of the cranial sutures.

He was treated by intravenous injections of 25 per cent solution of dextrose, intramuscular injections of magnesium sulfate and large doses of viosterol in oil.

His irritability diminished slowly, and his blood pressure remained about 120 systolic and 100 diastolic. During the third week a transient right wrist drop was noted. Even at the end of his three and a half week stay there were still a few stippled cells to be found in blood smears. He was discharged with the statement that a good deal of cerebral damage had probably been done.

A month later his blood pressure was 90 systolic and 40 diastolic, and he seemed happy and cheerful. At 14 months he was standing and saying "dada," and at 16 months he was noted by one of us (E. E. L.) to be acting like a 10 to 12 month old baby. At 19 months he seemed to all observers except the psychologist to have caught up with other babies of his age, but on psychologic examination he showed difficulties in dealing with space and direction, which persisted to the age of 5 years. His intelligence quotient at that time was 90.

The boy entered first grade at the age of 6 years and was promoted each year. At 7 years he had an intelligence quotient of 103. There was no evidence of visuomotor disability, and he could read and write well for his age.

CASE 19.—A 2 year old boy was admitted to the hospital because of weakness and limping of his left leg of one week's duration. He was delivered by forceps after a three day labor. He was weak after delivery and would not nurse. At 2 weeks of age he was taken to the Massachusetts Eye and Ear Infirmary, where he was treated for four weeks because of discharging eyes. He was discharged considerably below his birth weight, but at home he did well on formulas prescribed by another hospital (the nature of the formulas was not stated). Cod liver oil and orange juice had been taken in adequate amounts from early infancy.

He lived with his family in an old nine room house, in which the piping was entirely of lead. His father was a painter. The patient had been known to play with paint left about the house, though he had not been known to eat any.

His development was average. He held up his head at 3 months, sat up at 6 months and walked at 14 months. He was not talking, however, at 2 years.

A week before his admission to the hospital the patient showed a disinclination to walk and began to drag his left leg. The weakness became gradually more pronounced.

Physical examination revealed nothing remarkable save that in walking the left foot was not raised off the floor; the leg was rotated externally, and the foot dragged forward. The tendon reflexes were lively and approximately equal on the two sides; perhaps the reflex on the left side was somewhat livelier. The plantar reflexes were normal.

His blood showed a secondary anemia, with a hemoglobin content of 50 per cent by the Tallqvist method and a red cell count of 4,800,000. Several smears failed to show stippled cells.

Roentgenograms of the long bones showed dense bands at the ends of the shafts consistent with lead poisoning.

He was discharged unchanged after three weeks, on a high calcium diet with cod liver oil (3 drachms [11.7 Gm.] daily). No investigation of the water was made, but the parents were warned of the danger of allowing him to eat paint. A month later he returned to the outpatient department and was regarded as well.

A year later he returned because of pallor, irritability and loss of appetite. At this time he was definitely known to chew paint off objects, though his family tried to prevent him. The weakness of the leg had not recurred.

Physical examination disclosed nothing remarkable except pallor, which was confirmed by a hemoglobin content of 50 per cent, a red cell count of 2,600,000 and a smear showing moderate achromia but no stippled cells. Roentgenograms of the long bones again showed dense bands at the growing ends of the shafts. He was discharged on a high calcium diet with iron and ammonium citrate and cod liver oil (3 drachms [11.7 Gm.] daily). In a month his hemoglobin content was 80 per cent and his red cell count 4,000,000.

At 12 years he returned to the outpatient department because of enuresis. He gave a general impression of being dull. His mother gave the following report of his school progress: "He started to school at the age of 5 years. He spent two years in the first grade. The next year he had a teacher at home. The following year he spent in the second grade. He will start the fifth grade in the fall." Psychologic tests have not been given.

CASE 20.—A girl of 3 years was admitted to the hospital because of vomiting and abdominal pain of three months' duration. Her father and mother were separated at the time. Her birth and early development had been normal. She walked at 13 months and talked at 14 or 15 months. From the time she began to move about she chewed anything and everything, including paint from her crib and from window sills. About three months before her admission to the hospital she began to vomit, and the vomiting increased in frequency. A month later abdominal pain, irritability and pallor supervened. One month before admission strabismus was noted. During this period a gradual loss of weight occurred. She had complained of headache during the few days before admission.

On physical examination she was dull and drowsy. Her optic disks were noticeably choked, and her skull was hyperresonant on percussion. Her tendon reflexes were everywhere hyperactive, and Babinski signs were elicited on both sides.

Her hemoglobin level was 50 per cent; her red blood cell count was 2,600,000, and her blood smear showed achromia and 8 to 10 stippled cells per high power field. Her spinal fluid was under increased pressure and contained 18 cells per cubic millimeter and 108 mg. of total protein per hundred cubic centimeters.

Roentgen examination showed heavy bands at the growing ends of the long bones, consistent with lead poisoning, over a long period of time, with an especially heavy recent deposit.

Increasing drowsiness and vomiting continued in spite of treatment with hypertonic solution of dextrose (20 per cent) and dibasic sodium phosphate, and on her fifth hospital day bitemporal decompression was performed.

Frequent lumbar punctures were performed, with the removal of large amounts of spinal fluid (up to 200 cc. on one day), during the next four weeks. After that the patient gradually became interested in her surroundings, her vomiting stopped and she made a rapid recovery during the last two weeks of her stay. Six weeks after admission she was playing "normally" in bed, but psychometric examination showed a general level of intelligence around 3 rather than approaching 4 years, with special disabilities in the field of spatial relationship. She was discharged on the fifty-first day in the hospital, weak and underweight but able to walk and showing an active interest in life.

In spite of her mother's efforts she continued to eat paint at home, stripping all the paint off the porch railing before she was caught. A year later she was again admitted because of vomiting and abdominal pain. Her decompression wounds were bulging, but her optic disks were normal. Her gums showed a lead line. Her hemoglobin content was 53 per cent and her red blood cell count 3,900,000, with marked achromia and many stippled cells on smear. Spectroscopic examination of the blood showed a level "very much above anything found in normal controls." Roentgenograms of her long bones showed wide bands of lead deposit with recent accentuation at the growing ends. Roentgenograms of her skull showed no evidence of pressure. A lumbar puncture showed fluid under apparently increased pressure, with 6 monocytes per cubic millimeter and a total protein content of 46 mg. per hundred cubic centimeters. She was discharged on a high calcium diet and 18 drops of combined fish liver oils daily, and with assurance that she would be protected from paint in the future.

She was next seen when she was 9 years and 6 months of age, in response to a follow-up letter. Although she was friendly and outgoing, she was doing badly in school in the third grade, had a mental age of 7 7/12 years and an intelligence quotient of 80, with special defects in spatial orientation. Her score on the Ellis visual designs test was 1.5, which was below the calibrated level for her age.

319 Longwood Avenue.

RADIOACTIVE IODINE STUDIES IN CHILDHOOD HYPOTHYROIDISM

JOSEPH G. HAMILTON, M.D.

MAYO H. SOLEY, M.D.

WILLIAM A. REILLY, M.D.
AND
KARL B. EICHORN, M.D.
SAN FRANCISCO

The usefulness of radioactive isotopes of iodine in the study of iodine metabolism has been demonstrated by several groups of workers.[1] They are of particular value in measuring the gross iodine metabolism of the thyroid in situ [1b] in normal persons and in patients whose thyroids need not be removed surgically. The studies reported in this paper, which were carried out with the cooperation of the department of pediatrics of the University of California Medical School, show that by the use of radioactive iodine certain aspects of the iodine metabolism in children with hypothyroidism can be examined.

Ordinary, or stable, iodine and radioactive iodine are chemically and physiologically the same as long as the amount of radioiodine is less than that which produces physiologic changes by the action of its radiation. In these experiments, less than one-fiftieth the amount of radioiodine necessary to produce biologic changes was used. The radioactivity of a single dose of radioiodine enables one to follow its metabolic fate and to distinguish it from the iodine already present in the body. The radioiodine concentrated in the thyroid may be determined quantitatively without surgical removal of the gland, since the gamma rays emitted by it penetrate the overlying tissues and can be measured with a suitable detecting device, such as the Geiger-Müller counter.[1b] Thus, the addition of a trace of radioiodine to ordinary iodine serves to label all the iodine atoms in an administered sample.

The 10 children included in these studies had severe hypothyroidism as indicated by careful histories, physical examinations and pertinent laboratory tests (table 1). Three of them were less than 1 year old, and the remaining 7 ranged in age from

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The radioactive iodine was prepared through the cooperation of the radiation laboratory of the University of California.

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From the Radiation Laboratory of the University of California, Berkeley; the Divisions of Medicine and Pediatrics of the University of California Medical School and the Thyroid Clinic of the University of California Hospital, San Francisco.

1. (*a*) Hertz, S.; Roberts, A., and Evans, R. D.: Radioactive Iodine as Indicator in Study of Thyroid Physiology, Proc. Soc. Exper. Biol. & Med. **38**:510-513, 1938. (*b*) Hamilton, J. G., and Soley, M. H.: Studies in Iodine Metabolism of the Thyroid Gland in Situ by the Use of Radio-Iodine in Normal Subjects and in Patients with Various Types of Goiter, Am. J. Physiol. **131**:135-143, 1940; (*c*) Studies in Iodine Metabolism by the Use of a New Radioactive Isotope of Iodine, ibid. **127**:557-572, 1939. (*d*) Hamilton, J. G.; Soley, M. H., and Eichorn, K. B.: Deposition of Radioactive Iodine in Human Thyroid Tissue, Univ. California Publ., Pharmacol. **1**:339-368, 1940. (*e*) Hertz, S.; Roberts, A.; Means, J. H., and Evans, R. D.: Radioactive Iodine as an Indicator in Thyroid Physiology, Am. J. Physiol. **128**:565-576, 1940.

3½ to 19 years. None had received iodine or thyroid substance for six weeks or longer prior to the tests.

In the first experiment, iodine as sodium iodide containing a known amount of radioiodine, was administered orally in a dose of 14 mg. to each of the 8 older children and in a dose of 3.5 mg. to each of the 2 younger children. None of the patients had eaten for several hours prior to the ingestion of the experimental iodine. The counter tube of the Geiger-Müller counter was placed over the isthmus of the thyroid, and the uptake of iodine was measured as described in an earlier

TABLE 1.—*Data Concerning the Subjects*

Patient	Chronologic Age, Yr.	Age at Onset of Symptoms	I. Q. or M. A.	Epiphysial Age by Roentgenogram		Basal Metabolic Rate, %	Plasma Cholesterol, Mg. per 100 Cc.	Plasma Carotene, Mg.	Blood		
				C. A.	B. A.				Hemoglobin %	Hemoglobin Gm.	Red Cells
G. S.	½	5 ± mo.	2 ± mo.	3 mo.	0.3 mo.	—	253	—	70	10	4,200,000
D. B.	1½	Birth	53	8 mo.	3-5 mo.	—	284	—	98(Hel.)		4,060,000
M. M.	1⁷/₁₂	Birth	9.5 mo. (C.A. 17 mo.)	9 mo.	4.5 mo.	—45	256	—	57	8.3	2,900,000
G. W.	3½	Birth	.....	4 yr.	1-2 yr.	—	252	—	80	—	4,000,000
P. H.	4½	Birth	75	4½ yr.	2¾ yr.	Unsatisfactory	328	0.23	84(Hel.)		4,600,000
E. Z	7	Birth	69	4½ yr.	2 yr.	—37(av)	270	0.60	66	9.8	3,300,000
R. G..	8+	Birth	86 (C.A. 10 wk.) very retarded)	7 wk.	Newborn	—32	360	—	65(Hel.) (C.A. 7 wk.)		2,720,000
D. R..	10	1 ± yr.	73	5 yr.	2 yr.	—15	346	0.15	65 (C.A. 8 yr.)	—	4,100,000
E. P.	18	2 ± yr.	48	12 yr.	6 yr.	—59	282	0.30	58 (C.A. 12 yr.)	—	3,100,000
A. D.	19	1 to 2 yr.	50	12 yr.	2-6 yr.	—41	550	0.39	88	—	3,700,000

I.Q. indicates intelligence quotient; M.A., mental age; C.A., chronologic age; B.A., bone age. Chronologic age at the time various tests were performed is that given in column 2 unless otherwise indicated.

TABLE 2.—*Uptake of Iodine by the Thyroids of Hypothyroid Children After Ingestion of Two Doses of Radioactive Iodine (With and Without Carrier Iodine)*

Patient	Age, Years	Uptake of Iodine Five Days After Ingestion of 14 mg. (or 3.5 mg.), Percentage	Uptake of Iodine Five Days After Ingestion of About 1 Microgram, Percentage
G. S.	½	0.05	...
D. B.	1½	0.02	3.5
M. M.	1⁷/₁₂	0.50	...
G. W.	3½	0.05	...
P. H.	4½	2.20	52.0
E. Z.	7	0.10	4.5
R. G.	8	0.02	...
D. R.	10	0.10	3.5
E. P.	18	0.03	1.9
A. D.	19	0.55	30.0

report.[1b] Except in the 2 patients who had goiters (P. H. and A. D., table 1), the thyroid tissue took up so little of the labeled iodine that accurate measurements were impossible until the end of the fifth day after the iodine had been administered. At that time, nearly all the labeled iodine that had not been concentrated in the thyroids had been excreted, and hence did not interfere with determination of the radioiodine in the thyroids. In column 3 of table 2 are given the amounts of labeled iodine in the thyroids at the end of the fifth day, calculated as the percentage of the dose originally ingested. Only three of the thyroids accumulated 0.5 per cent or more, while two accumulated 0.1 per cent and the

remainder 0.05 per cent or less. In contrast, the thyroids of 5 normal adults five days after the oral ingestion of 14 mg. of iodine contained 4 per cent, and those of 3 normal children (4 to 10 years of age) retained 2 per cent of radioiodine.

The 3 children whose uptake was 0.5 per cent or more had palpable glands; 1 of them had a goiter which weighed approximately 50 Gm. as estimated by palpation. For patients A. D. and P. H., both of whom had goiters, reasonably accurate measurements could be obtained over the five days following the administration of a single dose of iodine (fig. 1). We were surprised to note that the type of curve was similar to that found in patients with hyperthyroidism.[1b] The uptake of iodine was rapid and was complete by the fourth hour. In the next twenty-four hours there was a rapid loss of about three fifths of the accumulated iodine, and during

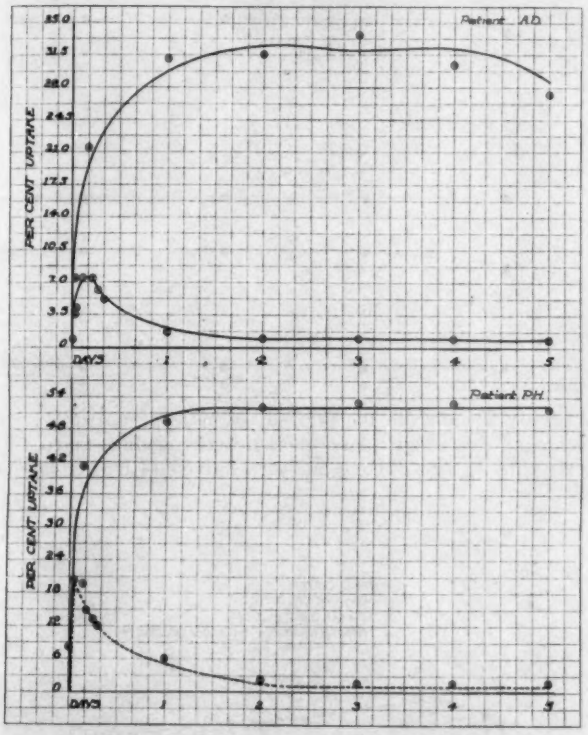


Fig. 1.—Uptake of radioactive iodine by the thyroids as measured in situ in patients A. D. and P. H. The abscissas indicate the time in days and the ordinates the percentage of the total dose of ingested iodine concentrated in the thyroids. In each curve the circles containing a dot indicate observations on a dose of 0.1 microgram of radioactive iodine administered on Feb. 5, 1940 and the circles containing a cross indicate observations on a dose of 14 mg. of radioactive iodine administered on April 21, 1941.

the succeeding four days a gradual loss of small amounts occurred. These 2 patients fall into a special group, since patients with goiter and severe hypothyroidism are rare in all regions except those in which goiter has been endemic for generations. Although the curves simulated those of hyperthyroidism, the character of the labeled iodine lost from the thyroids was not determined. If it were in the form of an active thyroid hormone, then such patients should be able to maintain themselves in a normal state of thyroid function provided sufficient iodine is absorbed. However, in neither of these patients has a sufficient trial of iodine

therapy alone been conducted. In the other patients, the thyroids apparently were incapable of accumulating enough iodine to maintain a normal balance.

A few months later, 6 of these patients, including the 2 with goiters, received a second oral dose of radioiodine in the form of sodium iodide without carrier

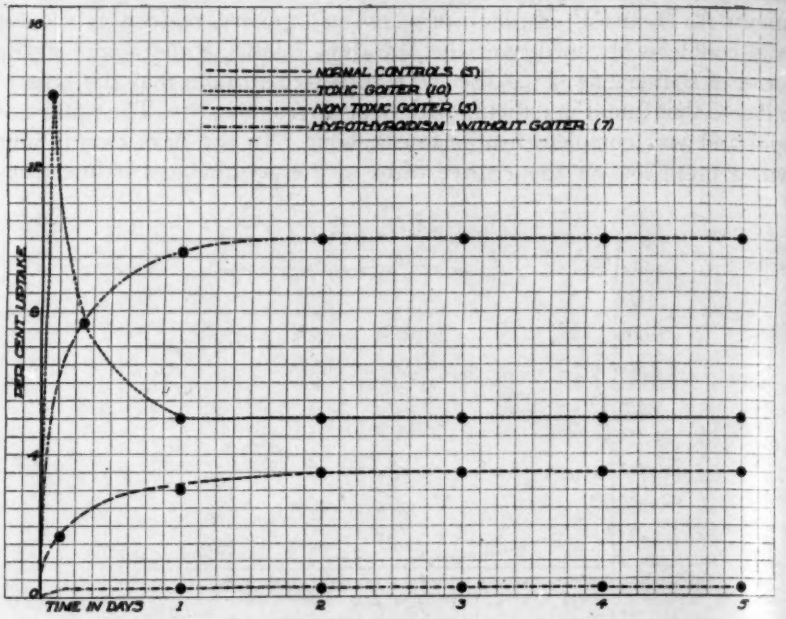


Fig. 2.—Uptake curves of iodine in the thyroids of patients measured in situ. The ordinate represents the percentage of a single dose of radioactive iodine taken up by the thyroids. The abscissa gives the time in days. Each subject received 14 mg. of labeled iodine.

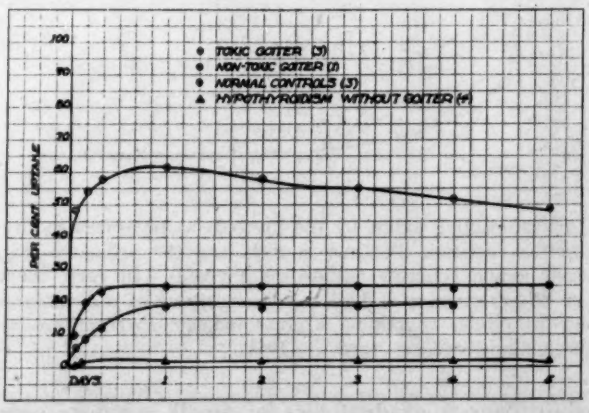


Fig. 3.—Uptake of radioactive iodine, given orally in a single dose of 0.1 microgram, in the thyroids of normal persons and of patients with various types of goiters.

iodine, so that the total for each patient was approximately 0.1 microgram of labeled iodine. In the 4 patients without goiters, the thyroids accumulated from 1.9 to 4.5 per cent of the labeled iodine by the end of the fifth day after its ingestion (table 2, column 4). It is apparent that thyroid tissue will take up a greater proportion of a small dose than of a large dose of iodine. The importance of this

fact is that by the use of extremely small amounts of radioiodine the presence of thyroid tissue may be detected in patients with hypothyroidism or myxedema. This test should demonstrate the presence of any thyroid tissue capable of concentrating iodine. We have not studied the effects of similar small doses of radioiodine on normal children. However, in 3 normal adults the average uptake of labeled iodine administered in a dose of approximately 0.0000002 Gm. was about 20 per cent, or

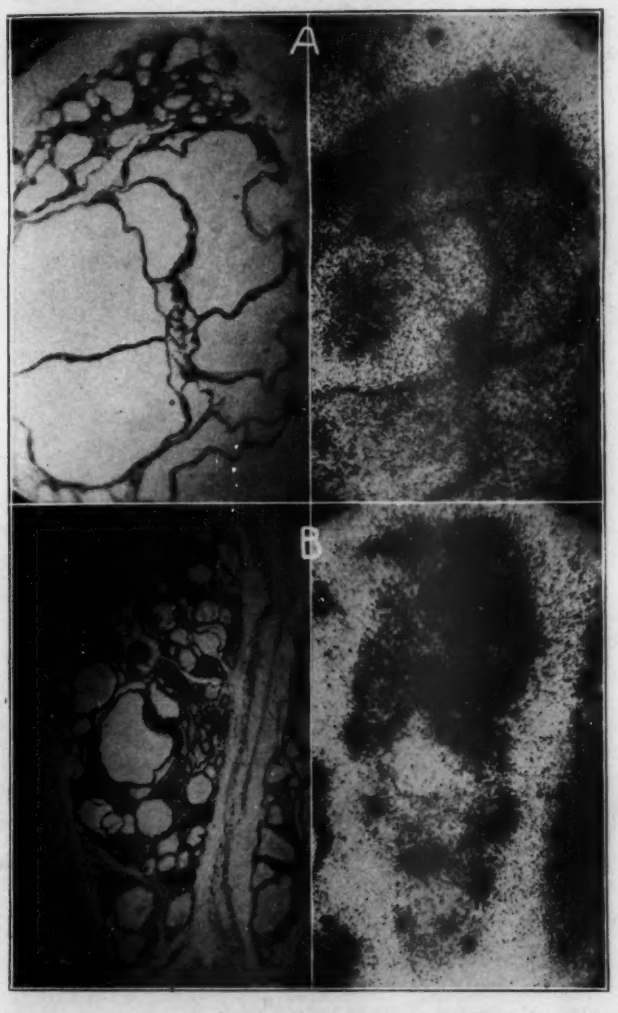


Fig. 4.—Sections of thyroid tissue from patient A. D. with their radioautograph. Note that most of the iodine is deposited in the cells of the acini rather than in the colloid.

from 4.5 to 10 times the uptake observed when a test dose of 14 mg. of labeled iodine was employed.

After retest with a dose of approximately 0.1 microgram of labeled iodine, the uptake curves of the 2 patients with goiter and hypothyroidism were similar to those of patients with toxic goiter (compare the curves of figures 1 with curves of patients with other thyroid diseases, figures 2 and 3). The maximum uptake in patient P. H., the child with a goiter weighing about 50 Gm., was about 53 per cent, while in patient A. D., the child with a slightly enlarged thyroid, the uptake was

about 33 per cent. Specimens of the thyroids of both patients were taken for biopsy, and radioautographs were made according to the technic reported elsewhere [14] (figs. 4 and 5). The specimen from patient P. H., taken from the isthmus of the thyroid (to relieve pressure symptoms), showed atrophy with incomplete formation or rupture of many of the acini, little colloid, which stained poorly with hematoxylin and eosin, and acinal cells which varied in size and usually

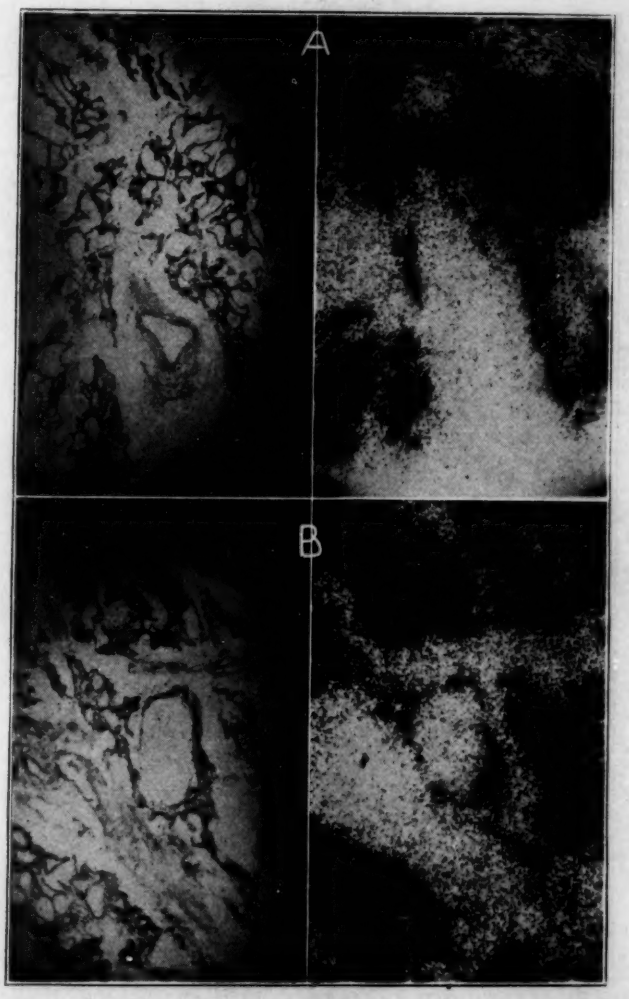


Fig. 5.—Sections of thyroid tissue from patient P. H. with their radioautographs. Note the "feathery" appearance of the acini and the relatively large amounts of iodine in the cells rather than in the colloid.

were pale and flattened. No lymphocytes, nodules or appreciable fibrosis were noted. The blood vessels were thin walled and contained no blood. The sections from the thyroid of patient A. D. showed a somewhat similar histologic picture but had more the appearance of an involuted gland. The radioautographs demonstrated that in both subjects most of the iodine was deposited in the cells of the acini rather than in the colloid and that surprisingly large amounts of iodine were concentrated in the thyroid. One must assume that some fault prevents the release

of an active thyroid hormone from the accumulated iodine; otherwise, these patients should not have had the severe degree of hypothyroidism which was obvious even on casual clinical examination. The accompanying photograph of patient A. D. (fig. 6) shows his characteristic cretinoid appearance.

Some of the thyroid tissue from patients A. D. and P. H. was analyzed in order to determine the amount of radioactive iodine in the form of thyroxine, diiodotyrosine and inorganic iodine. These goiters had been removed forty-eight hours after the administration of radioactive iodine. Iodine fractionations were done by Dr. I. Perlman,[2] following technics employed in studying sheep's thyroids. Table 3 shows that about one fifth of the iodine was in the form of thyroxine.

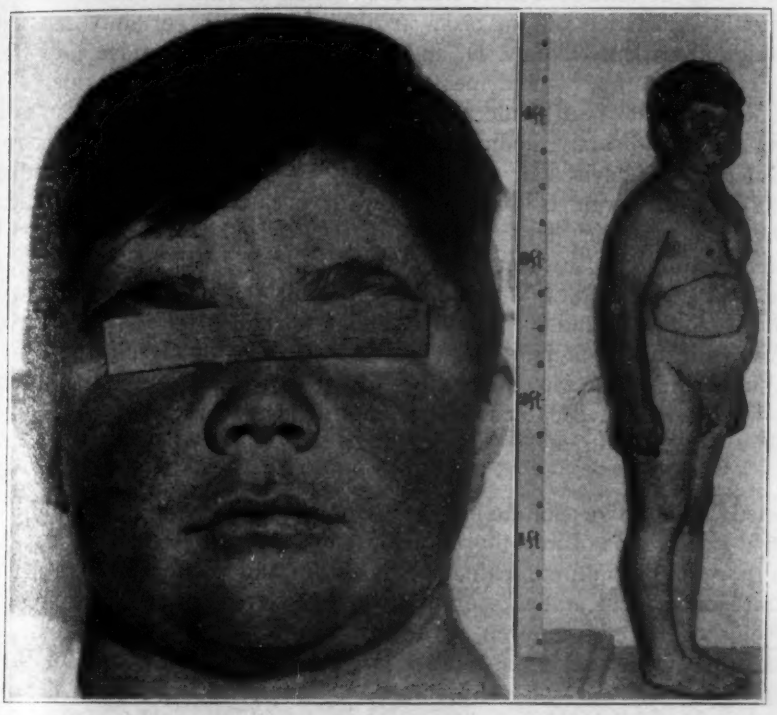


Fig. 6.—Patient A. D. at the age of 18 years. His appearance is characteristic of childhood myxedema.

TABLE 3.—*Results of Iodine Fractionations*

Subject	Sample	Amount of Thyroid Tissue Analyzed, Gm.	Thyroxine Iodine, Percentage	Diiodotyrosine Iodine, Percentage	Inorganic Iodine, Percentage
A. D.	First	0.188	12.1	60.5	18.2
	Second	0.175	11.4	57.9	18.5
P. H.	First	1.087	16.4	52.3	22.1
	Second	1.332	12.1	52.0	20.0

The thyroxine fraction probably was retained in the gland; otherwise these children would have maintained themselves in normal thyroid balance.

2. Perlman, I.; Morton, M. E., and Chaikoff, I. L.: Radioactive Iodine as Indicator of Metabolism of Iodine: Rates of Formation of Thyroxine and Diiodotyrosine by Intact Normal Thyroid Gland, J. Biol. Chem. **139**:449-456, 1941.

COMMENT

Many of the assumed fundamental changes in the patients we have studied are a matter of speculation. Although we have no final pathologic description of the thyroids of the hypothyroid children (without goiter), the function of the glands, as measured by their inability to maintain a normal thyroid balance and to take up more than a fraction of the normal amount of iodine, apparently is as inefficient as in spontaneous myxedema of adults. It is known that the thyroids of patients with adult myxedema are fibrosed, atrophied and nonfunctioning. In other words, the results are what might have been predicted from previous knowledge.

In the 2 goitrous children, a state of hypothyroidism existed even though the thyroids of both accumulated more than the normal amount of iodine. One control study should be carried out in order to determine with certainty the failure of the thyroids of patients like A. D. and P. H. to release hormone into the circulation. This, of course, is the measurement of circulating thyroxine. To date, such studies have not been made because of technical difficulties in separation and measurement of radioactive iodine in the blood, although such measurements are possible if methods devised by Salter, Bassett and Sappington [3] are modified. If the circulating thyroxine is extremely low or even absent in such patients, the metabolic fault must lie in the inability of the thyroid to release, rather than in its inability to produce, this hormone.

It is strange, indeed, that the metabolism in respect to uptake curves and deposition of iodine within the gland is similar to that in the hyperplastic thyroids of patients with toxic goiters. Thus, that the extremes of thyroid function exhibit certain similarities is a fact susceptible to no further interpretation today than when it was first pointed out many years ago by David Marine.

SUMMARY

Labeled (radioactive) iodine has been employed to determine the ability of the thyroids in two groups of hypothyroid children to concentrate iodine.

The thyroids of children with hypothyroidsm and without goiters are able to concentrate only small amounts of orally administered iodine, as compared with the thyroids of normal children or adults. In these hypothyroid children, the remaining thyroid tissue concentrated a larger precentage of a dose of 0.1 microgram than of a dose of 14 mg. of iodine.

The thyroids of 2 children with goiters and with severe hypothyroidism took up relatively large amounts of iodine and by chemical analysis contained both thyroxin and diiodotyrosine in considerable quantities. The uptake curves of the thyroids as measured in situ were similar to those seen in hyperthyroidism in adults. Radioautographs made from sections of the thyroids of both of these children indicate that by the fifth day after the oral administration more of the iodine was in the cells than in the colloid.

University of California Medical School.

3. Salter, W. T.; Bassett, A. M., and Sappington, T. S.: Protein-Bound Iodine in Blood: Its Relation to Thyroid Function in One Hundred Clinical Cases, Am. J. M. Sc. **202**:527-542, 1941.

REGULATION OF LEVEL OF VITAMIN A IN BLOOD OF NEWBORN INFANTS

J. M. LEWIS, M.D.
NEW YORK

CAPTAIN O. BODANSKY
MEDICAL CORPS, ARMY OF THE UNITED STATES
AND

L. M. SHAPIRO, M.D.
NEW YORK

PART 1

In previous communications [1] we reported that the concentration of vitamin A in the blood gave some indication of the degree of vitamin A storage in the body. Thus, low blood levels were usually associated with little or no storage in the liver of the rat, whereas high blood levels were accompanied by large stores; intermediate blood levels were of less significance, inasmuch as they were found to be associated with both large and small amounts of vitamin A in the liver.

The results of studies which we carried out on infants coincided, in general, with those obtained in studies on rats and indicated the practical importance of the blood level of vitamin A in the estimation of the vitamin A status of a subject. In febrile conditions, however, there is a rapid lowering of the vitamin A concentration in the blood, which is not necessarily accompanied by poor storage of the vitamin in the liver. It is not definitely known whether high temperature brings about destruction of the vitamin in the blood; whether, as a result of fever, there is an increased demand by the tissues for the vitamin, or whether there is an interference in the mobilization of vitamin A from the liver.

In the present communication it will be demonstrated that the generalization "abnormally low levels of vitamin A in the blood indicate poor storage" does not hold during the newborn period. The results of experiments bearing on the causation of the diminished concentration of vitamin A in the blood of newborn infants will also be reported.

Determinations of vitamin A (and carotene) were carried out on the blood of 108 normal newborn infants. The blood was obtained throughout the newborn period from the superior sagittal sinus except at birth, when cord blood was used for determination of the vitamin A and carotene levels. The method employed for these analyses has been fully described elsewhere.[1c]

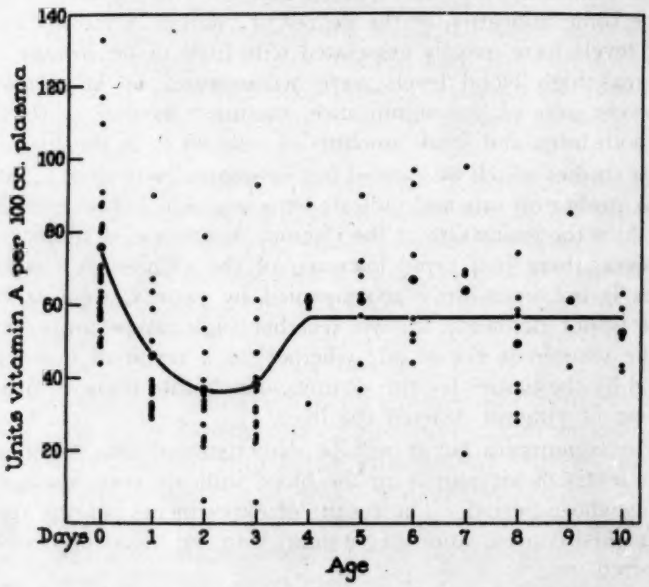
The results of the determinations of vitamin A are plotted in the chart. It will be noted that there was a sharp drop in the concentration of the vitamin in the blood during the first two days of life, from an average value of 76 U. S. P. units per hundred cubic centimeters of plasma at birth to 37 units at the end of

From the Department of Pediatrics, New York University College of Medicine, and the Departments of Pediatrics and Obstetrics, Beth Israel Hospital.

1. (*a*) Lewis, J. M.; Bodansky, O.; Falk, K. G., and McGuire, G.: Relationship of Vitamin A Blood Level in the Rat to Vitamin A Intake and to Liver Storage, Proc. Soc. Exper. Biol. & Med. **46**:248, 1941; (*b*) Vitamin A Requirement in the Rat: The Relation of Vitamin A Intake to Growth and to the Concentration of Vitamin A in the Blood Plasma, Liver and Retina, J. Nutrition **23**:351, 1942. (*c*) Lewis, J. M.; Bodansky, O., and Haig, C.: Level of Vitamin A in the Blood as an Index of Vitamin A Deficiency in Infants and in Children, Am. J. Dis. Child. **62**:1129 (Dec.) 1941.

forty-eight hours. This low level was maintained for one day, and on the fourth day the vitamin A concentration rose to 61 units, a value which was maintained throughout the remainder of the newborn period.

The question may be raised whether the vitamin A content of cord blood represents the true level of vitamin A in the blood of the infant at birth. We therefore compared the concentration of vitamin A (and of carotene) in cord blood and in blood obtained from the infant by puncture of the superior sagittal sinus within twenty minutes after birth. Results of these analyses as well as of analyses of maternal blood may be observed in table 1. It will be seen that the vitamin A and carotene content of blood obtained from the umbilical cord was about the same as of that obtained from the superior sagittal sinus. It is interesting to note that the concentration of vitamin A in the blood of the infant was not significantly different from that in the blood of the mother, whereas the carotene content was much lower than that of the maternal blood. The poor diffusion of carotene



The vitamin A concentration in the blood during the first ten days of life.

TABLE 1.—*Concentration of Vitamin A and of Carotene in Cord Blood and in Blood Obtained Directly from the Infant and from the Mother* *

Infant	Vitamin A in Blood Plasma, U.S.P. Units per 100 Cc.			Carotene in Blood Plasma, Mg. per 100 Cc.		
	Cord	Infant	Mother	Cord	Infant	Mother
Tu	63	57	72	0.018	0.018	0.113
Ja	57	64	69	0.014	0.011	0.151
Gr	88	73	77	0.018	0.019	0.061

* Blood was obtained from the infant and from the mother within twenty minutes after delivery.

through the placenta as compared with that of vitamin A may be due to the fact that carotene has a larger molecule, having twice the molecular weight of vitamin A. It may be added that the carotene content of the blood remains low throughout the whole newborn period.

The frequency with which values below 40 units occurred during the first three days of life was striking. Thus, 64 per cent of infants of this age group had concentrations of vitamin A in the blood lower than 40 units, whereas only 17 per cent of infants from 4 to 10 days old had these low blood levels. In this connection it is of interest to add that when febrile diseases were excluded values below 40 units were encountered in older infants only under exceptional circumstances, as, for example, when there was an interference in the absorption of the vitamin (cystic fibrosis of the pancreas, congenital obliteration of the bile ducts, celiac disease) or when a diet almost devoid of vitamin A had been administered for many weeks.

In depletion experiments carried out on rats [1b] we found that the concentration of vitamin A in the blood dropped to low levels (below 40 units) only when the livers were devoid or almost devoid of vitamin A. On the other hand, when there was adequate storage of vitamin A the blood concentrations were maintained at good levels for months at the expense of the vitamin A stores in the livers. Infants receiving diets devoid of vitamin A maintained blood levels above 40 units for many weeks, at the end of which time the concentration of vitamin A in the blood dropped, presumably because of the depletion of vitamin A stores. When infants were given large quantities of vitamin A in order to increase their stores and were then fed vitamin A–free diets, blood concentrations were maintained at high levels for months, in spite of the administration of diets devoid of vitamin A.[1c]

TABLE 2.—*Vitamin A Content of the Livers of Newborn Infants*

Number of Livers Analyzed	Average Number of Vitamin A Units (U.S.P.) per Gm. of Liver	Average Number of Vitamin A Units (U.S.P.) per Liver
24	134	12,770

The pronounced decrease in the vitamin A content in the blood of newborn infants was surprising in view of the fact that we found that the liver, the main storehouse of vitamin A, contained considerable quantities of the vitamin in the newborn period. In table 2 are recorded the results of the vitamin A analyses of 24 livers of infants dying at birth or shortly thereafter. The average value per liver was found to be 12,770 U. S. P. units, or 134 units per gram of liver.[2]

There is no evidence that the tissues of newborn infants utilize vitamin A or any of the other vitamins to a greater degree than do those of older infants. As a result of the aforementioned depletion experiments on rats and on infants, it seemed to us that the sharp fall of vitamin A in the blood during the first few days of life, in spite of the abundance of vitamin A in the liver, was an indication that the mechanism governing the release of vitamin A from the liver (as well as from other stores) is not fully developed in the newborn infant. To test the validity of this view, we decided to give newborn infants a diet devoid of vitamin A and to carry out analyses of blood early and late in the newborn period. If the blood concentrations of vitamin A were found to rise spontaneously to normal levels late in the newborn period, while the vitamin A–free diet was being fed, then the conclusion would be warranted that the increased content of the vitamin in the blood must

2. These values are higher than those previously reported from Holland by Wolff (Wolff, L. K.: On the Quantity of Vitamin A Present in the Human Liver, Lancet **2**:617, 1932), who obtained an average of 42 U. S. P. units of vitamin A per gram of liver for newborn infants. It may well be that the diets of the pregnant women in our series contained larger quantities of vitamin A and, as a result, the livers of their newborn infants had larger amounts of vitamin A.

have come from the stores in the body. As a corollary, the failure to maintain normal levels during the first few days of life could then be attributed to a transient lack of mobilization of vitamin A from its stores.

Accordingly, 15 newborn infants were given twelve hours after birth a special preparation of milk, the butter fat of which was replaced by a vegetable oil. This product thus contained no vitamin A.[3] When the infants were 2 to 3 days old, determinations of vitamin A were made. Eleven of the 15 infants were found to have values below 40 units, and for them use of the vitamin A–free diet was continued throughout the newborn period. Analyses of the blood were again carried out from the sixth to the ninth day of life.

The results of this experiment are recorded in table 3, where it will be seen that there was a spontaneous rise in the vitamin A concentration of the blood in 10 of 11 infants during the latter part of the newborn period; in 8 instances the

TABLE 3.—*Concentration of Vitamin A in the Blood of Newborn Infants Receiving a Vitamin A-Free Diet* *

Infant	Vitamin A in Blood Plasma, U.S.P. Units per 100 Cc., at Age of	
	1-3 Days	6-9 Days
Bg	24	63
Ee	23	67
Gh	28	53
Gl	32	27
Lr	6	49
Or	29	42
Mw	21	32
Pf	33	47
Pg	27	34
Ls	37	57
Fb	6	49
	—	—
Average	24	47

* For this experiment were selected infants whose blood values were below 40 units per hundred cubic centimeters of plasma during the first three days of life.

values exceeded 40 units per hundred cubic centimeters of plasma. The average blood level for the 11 infants early in the newborn period was 24 units, whereas late in the newborn period it rose to 47 units despite the consumption of a vitamin A–free diet. It should be added that these infants tolerated the special preparation of milk well and gained as satisfactorily as those receiving the usual milk formula.

COMMENT

These observations, therefore, indicate that the mechanism controlling the mobilization of vitamin A from the liver as well as from other organs storing vitamin A is not fully developed during the first few days of life. It may be recalled that the liver exhibits other manifestations of hypofunction during this stage. For example, bilirubin increases in the blood early in the newborn period because of the failure of the liver to excrete this substance satisfactorily, and, as a result, physiologic jaundice develops.

The fall in prothrombin level of the blood of the newborn infant parallels that of vitamin A, and a rise occurs spontaneously in the latter part of the newborn period, even in conditions which militate against the ingestion or absorption of

3. Analysis of this preparation in our laboratory revealed an absence of vitamin A.

vitamin K, as, for example, in esophageal atresia and in congenital obliteration of the bile ducts.[4] In view of our observations, it is quite possible that the liver of the newborn infant contains vitamin K or prothrombin but cannot mobilize these substances. This aspect of the vitamin K problem in the newborn infant is worthy of investigation and is being studied in our laboratory. A similar situation may exist in regard to the mobilization of glycogen during the newborn period. Thus, it has been shown by McKittrick [5] as well as by other investigators that the blood sugar drops to low levels during the first days of life. This occurs despite the fact that the liver of the newborn infant contains glycogen. It has been shown, however, that glycogen in the newborn infant exhibits marked stability, so that relatively large amounts of epinephrine are required for its mobilization from the liver.[6] In newborn rats and guinea pigs, also, glycogen can be mobilized by epinephrine only with difficulty during the first few days of life.[7]

It is probable that other organs besides the liver do not assume normal function immediately after birth. In this connection, it is of interest to add that Bakwin [8] has recently presented evidence indicating that the lowering of blood calcium in the newborn infant is due to a transient hypofunction of the parathyroid glands.

PART 2

That a lack of release of vitamin A from its stores during the first few days of life may not be the only factor in bringing about low levels of vitamin A is apparent when it is recalled that the intake of milk, and therefore of vitamin A, is extremely low during this period. To what extent this low intake of vitamin A is also a factor in the pathogenesis of the low blood concentrations of vitamin A during the newborn period was considered worth investigating.

Eight infants were given 2 drops of halibut liver oil (2,500 U. S. P. units) twelve hours after birth and again on the second day in order to determine whether an increase in the intake of vitamin A would prevent the lowering of the vitamin concentration in the blood. When these infants were 3 days old samples of blood for vitamin A analysis were taken twenty-four hours after the last administration of halibut liver oil to assure a postabsorptive level.

In table 4 the results of these analyses are shown. In 4 of the 8 infants, the administration of the vitamin A supplement failed to maintain blood levels above 40 units per hundred cubic centimeters of plasma, the average concentration for the entire group of 8 infants being 36 units, a value comparable to that obtained for infants receiving the usual formulas unsupplemented with vitamin A. It will also be noted that late in the newborn period the vitamin A concentration was about the same in this group as in infants receiving no supplement.

In order to determine whether the lack of rise in the blood level was due to a failure of absorption of the vitamin concentrate, the meconium of 2 infants was collected for a period of forty-eight hours and assayed for vitamin A. These analyses indicated that there was no apparent failure of absorption, for only 3 per cent of the concentrate could be accounted for in the intestinal excreta. It might be

4. Sanford, H. H., and Shmigelsky, I.: Is the Presence of Bile and Food in the Small Intestine Necessary for the Formation of Prothrombin? Am. J. Dis. Child. **63**:894 (May) 1942.

5. McKittrick, J. B.: Serial Blood Sugar Determinations in Normal Newborn Infants, J. Pediat. **16**:151, 1940.

6. Van Creveld, S.: Glycogen Disease, Medicine **18**:1, 1939.

7. Wertheimer, E.: Stoffwechselregulationen; Die Sonderstellung der Kohlehydratbestände in Zellen mit starker Wachstumfähigkeit, Arch. f. d. ges. Physiol. **223**:619, 1929.

8. Bakwin, H.: Tetany in Newborn Infants: Relation to Physiologic Hypoparathyroidism, J. Pediat. **14**:1, 1939.

added that the excretion of vitamin A in the feces of older infants was also found to be about 3 per cent when concentrates containing 12,000 units of vitamin A were given.

Another indication that the vitamin A supplement was well absorbed by the newborn infant may be seen in table 5, where the results of analyses of the blood four hours after the administration of the halibut liver oil are recorded. Seven of the 8 infants had blood levels of vitamin A higher than 40 units, and 3 had concentrations over 100 units, the average value for the entire group being 80 units, as

TABLE 4.—*Vitamin A Concentration in the Blood of Newborn Infants Receiving Supplements of Halibut Liver Oil (2,500 Units) for the First Two Days of Life*

Infant	Vitamin A in Blood Plasma, U.S.P. Units per 100 Cc., at Age of	
	3 Days*	8-10 Days
Ks	38	59
Ps	11	42
Rk	44	54
Bl	54	85
Js	6	38
Pf	49	54
Cs	16	57
Fb	73	58
	—	—
Average	36	56

* Blood samples were taken twenty-four hours after the last dose of the oil.

TABLE 5.—*Vitamin A Concentration in the Blood of 2 and 3 Day Old Infants Four Hours After Administration of 2,500 Units of Vitamin A*

Infant	Age, Days	Vitamin A in Blood Plasma, U.S.P. Units per 100 Cc.
Tf	2	120
Mw	2	50
Km	3	31
Bu	2	80
Sh	3	136
Ms	2	56
Ra	3	55
Ca	3	114
		—
	Average	80

contrasted with 36 units, the value obtained twenty-four hours after the administration of halibut liver oil.

The fate of the absorbed vitamin A is a matter of speculation. As there is no evidence that vitamin A is destroyed in the blood, two possibilities exist: (1) that it was almost completely stored, only minimal amounts being utilized by the tissues, or (2) that some of the absorbed vitamin A was stored, a considerable fraction being used up by the tissues. We are inclined to favor the first possibility for the following reason: If most of the absorbed vitamin had been utilized by the tissues, then it would seem that the tissue requirement for vitamin A would have been met, in part at least, and one would not expect the blood concentration to have fallen in twenty-four hours to the same levels as in infants

receiving no vitamin supplement. It would therefore seem that the function of storage of vitamin A, in contrast to its mobilization, is not affected early in the newborn period.

The fact that the concentration of vitamin A in the blood was high four hours after the ingestion of the concentrate makes it obvious that frequent administration of vitamin A during the day will prevent an excessive fall in the vitamin A content of the blood during the first few days of life. In this connection it should be recalled that milk, when taken in adequate amounts, is a good source of vitamin A and supplies the infant with this vitamin every three or four hours, depending on the interval between feedings. We therefore studied the effect on the blood level of adding vitamin A directly to the formulas given infants during the first three days of life. In order to make sure of uniform distribution of the vitamin in the milk we made use of a solution of the vitamin in propylene glycol.[9]

TABLE 6.—*Concentration of Vitamin A in the Blood of 3 Day Old Infants Receiving a Supplement of Vitamin A in the Daily Formula* *

Infant	Vitamin A in Daily Supplement, U.S.P. Units	Vitamin A in Blood Plasma, U.S.P. Units per 100 Cc.
Po	2,000	67
Go	2,000	110
Bt	2,000	85
Pa	2,000	68
Se	2,000	71
My	2,000	60
Wa	500	55
Co	500	93
Ma	500	49
Ke	500	55
Lu	500	46
Go	500	37
Ch	500	53
	Average	65

* Supplementing the formula with vitamin A was begun on the first day of life.

Thirteen infants were given 500 or 2,000 units of vitamin A incorporated in the daily formula, which contained 4 ounces (120 cc.) of whole milk. Since the milk itself supplied about 200 units of vitamin A (1 ounce [30 cc.] of milk has an average vitamin A content of 50 units), the total intake of vitamin A was 700 or 2,200 units. Use of the formulas was begun twelve hours after birth, and when the infants were 3 days old the vitamin A content of their blood was determined at various times between feedings.

The results of this experiment are shown in table 6, in which it will be observed that the blood level of vitamin A remained above 40 units in 12 of 13 infants 3 days old. The average value for the group as a whole was 65 units. Infants receiving the 2,000 unit supplement had an average concentration of 77 units, and those receiving only 500 units an average of 55 units.

COMMENT

The low intake of vitamin A during the first few days of life may therefore be regarded as a second factor responsible for the low levels of vitamin A in the blood.

9. This product was prepared for us by Dr. O. Barlow, of the Winthrop Chemical Company.

There is no evidence at the present time that the low level of vitamin A in the blood brings about any pathologic disorder in the newborn infant. The prevention of these low concentrations of vitamin A in the blood by frequent administration of vitamin A therefore seems unnecessary.

SUMMARY AND CONCLUSIONS

The concentration of vitamin A in the blood was determined for 108 infants throughout the newborn period. The results revealed a sharp drop in the blood level of the vitamin during the first forty-eight hours of life and a rise to a normal level on the fourth day.

Experiments undertaken to determine the cause of the low concentration of vitamin A in the blood during the first three days of life indicated that two factors are involved: (1) the failure of the liver (as well as other organs storing vitamin A) to mobilize adequate amounts of the vitamin, and (2) the low intake of vitamin A.

There is no evidence that a low level of vitamin A in the blood early in the newborn period brings about any pathologic disorder. The prevention of the marked lowering of the vitamin A content of the blood by frequent administration of a vitamin A concentrate therefore seems unnecessary.

Miss M. Gray cooperated in this study.

25 East Eighty-Third Street.

1 West Seventy-Fourth Street.

EFFECT OF MATERNAL RACHITOGENIC DIET ON SKELETAL DEVELOPMENT OF YOUNG RAT

JOSEF WARKANY, M.D.
CINCINNATI

The effect of maternal rachitogenic diets on the skeleton of the fetus in rats has been studied by various methods. Toverud [1] stated that female rats fed a low calcium diet did not breed sufficient offspring to permit study of the effect of the diet. Korenchevsky and Carr [2] found the chemical composition of the young of mothers fed a diet deficient in fat-soluble factors identical with that of the offspring of control animals. These authors expressed the opinion that the normal chemical composition of the fetuses born of mothers fed the deficient diet could be accounted for by "the fact" that the maternal organism will so far as possible yield all the necessary substances to the offspring by the sacrifice of its own tissue. These early experiments illustrate the chief difficulty encountered in attempts to produce prenatal deficiency diseases in the young by feeding a deficient diet to the mother. In severe deficiency, breeding does not take place; if the deficiency is mild, the young are normal at birth. A similar opinion was expressed by Macomber,[3] who found that a maternal diet low in calcium affected fertility by increasing the intrauterine mortality. The young who were carried to term were found to be normal at birth both in weight and in calcium content. According to this author, pregnancy in the rat makes relatively small demands on the mothers "because the young are largely cartilaginous at birth." In contrast to the investigators cited above, Shipley, Park, McCollum and Simmonds [4] demonstrated that if rats were held for several generations to a diet low in calcium, the skeletons of the young became progressively more slender. The ribs in the animals of the fourth generation became so fragile that hundreds of fractures occurred. In an extensive study on the mineral composition of the young rat Cox and Imboden [5] showed that the composition of the young of mothers fed diets of various mineral contents was within the range observed in the offspring of stock rats. However, when the maternal diet was excessively high in calcium and unbalanced in regard to phosphorus, the composition of the newly born rat was adversely affected. On a diet of a calcium: phosphorus ratio of 5.0, a lowered ash content of the young after several successive reproductive cycles was observed. These authors were of the opinion that the young showed evidence of congenital rickets. However, anatomic or histologic studies are not included in this report. The observations

From The Children's Hospital Research Foundation and the Department of Pediatrics of the College of Medicine of the University of Cincinnati.

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2. Korenchevsky, V., and Carr, M.: Influence of an Excessive Amount of Fat-Soluble Factor and Calcium in the Mother's Diet During Pregnancy, Biochem. J. **18**:1313, 1924.

3. Macomber, D.: Effect of a Diet Low in Calcium on Fertility, Pregnancy and Lactation in the Rat, J. A. M. A. **88**:6 (Jan. 1) 1927.

4. Shipley, P. G.; Park, E. A.; McCollum, E. V., and Simmonds, N.: Studies on Experimental Rickets: VII. The Relative Effectiveness of Cod Liver Oil as Contrasted with Butter Fat for Protecting the Body Against Insufficient Calcium in the Presence of a Normal Phosphorus Supply, Am. J. Hyg. **1**:512, 1921.

5. Cox, W. M., and Imboden, M.: The Mineral Composition of Young Rats, J. Nutrition **11**:177, 1936.

of Cox and Imboden were confirmed by Bodansky and Duff,[6] who investigated the dependence of fetal growth and storage of calcium and phosphorus on the parathyroid function and diet of pregnant rats. Sontag, Munson and Huff[7] reported that the offspring of rats fed a diet deficient in calcium and phosphorus during pregnancy have a lower content of these minerals than those born of control rats fed an adequate diet. Sugiyama[8] obtained three litters from 1 rat fed the Steenbock and Black[9] diet 2965. In the newly born young this author found some histologic signs of rickets. I have undertaken similar experiments.

EXPERIMENTAL MATERIALS AND METHODS

In preliminary experiments female rats of the Sprague-Dawley strain aged 3 to 5 months and fed the Steenbock and Black diet 2965 were mated with males of the same strain. A single litter could occasionally be obtained from such rats, but successive matings rarely took place. The offspring appeared normal externally and also after clearing by the Dawson[10] method. Histologic examination of the skeleton of the offspring was not made. It was thought that a modification of the Steenbock and Black diet 2965 which would increase the fertility of mothers fed this diet without interfering with its rachitogenic effect might lead to skeletal changes in the young. The addition of 2 per cent of dried pig liver to the Steenbock and Black formula makes this diet more adequate for female rats of the reproductive age. The fertility of the rats is much improved with this "diet R," which has the following percentage composition: yellow corn meal 76, wheat gluten 18, calcium carbonate (chemically pure) 3, sodium chloride (chemically pure) 1 and dried pig liver 2. The calcium: phosphorus ratio of diet R is about 6.0. The small amounts of phosphorus and traces of vitamin D contained in the pig liver do not impair the rachitogenic effect of the diet. This was shown in preliminary experiments in which rats fed diet R for three weeks after weaning acquired severe rickets.

Twenty-three female rats of the Sprague-Dawley strain were placed on diet R at the age of 3 months. When daily vaginal smears revealed regular estrus cycles, the animals were mated with normal males of the same strain which had been fed an adequate stock diet. As a rule, the first mating took place after the females had been on diet R for two weeks.

Of these 23 females 1 died before mating. Three became pregnant but died before term. Nineteen females went through a successful first pregnancy and delivered their young at term. Sixteen females delivered second and 5 of these third litters. One female had a fourth and a fifth litter. These forty-two litters consisted of 294 young, all of which appeared externally normal. Two hundred and forty-eight of these young were cleared by the Dawson[10] method, which permits a visualization of the osseous skeleton. Of the cleared specimens, 136 appeared normal while 112 showed gross skeletal deformities.

RESULTS

Figure 1 *A* shows a cleared normal newly born rat. The osseous parts of the radius, ulna and tibia appear as straight rods; the fibula is slightly curved. While the proximal ends of the tibia and fibula are somewhat separated, their distal ends are closely united. The ribs represent bony arches which in their downward and forward descent become continuously somewhat broader.

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6. Bodansky, M., and Duff, V. B.: Dependence of Fetal Growth and Storage of Calcium and Phosphorus on the Parathyroid Function and Diet of Pregnant Rats, J. Nutrition **22**: 25, 1941.

7. Sontag, L. W.; Munson, P., and Huff, E.: Effects on the Fetus of Hypervitaminosis D and Calcium and Phosphorus Deficiency During Pregnancy, Am. J. Dis. Child. **51**:302 (Feb.) 1936.

8. Sugiyama, B.: Studies on Experimental Rickets: On Appearance of Experimental Rickets in the Embryonic Period, Orient. J. Dis. Infants **21**:27, 1937.

9. Steenbock, H., and Black, A.: Fat-Soluble Vitamins: XXIII. The Induction of Growth-Promoting and Calcifying Properties in Fats and Their Unsaponifiable Constituents by Exposure to Light, J. Biol. Chem. **64**:263, 1925.

10. Dawson, A. B.: Note on the Staining of the Skeleton of Cleared Specimens with Alizarin Red S, Stain Technol. **1**:123, 1926.

The deformed specimens (fig. 1 *B* and *C*)—offspring of mothers fed diet R—in the cleared stage show a pronounced curving of the radius, ulna, tibia and fibula; the convexities point toward the dorsa of the forearms and legs. The sharp bend of the radius is usually near its proximal end. The ulna, which is longer than the radius, curves around the distal end of the radius, as illustrated in figure 1 *C*. The humerus is shortened, and its distal end shows cupping. The first three or four ribs present a peculiar angulation in their osseous parts, and their distal ends become abruptly broader at the point of angulation. The tibia is thick, short and bent. The fibula runs parallel to the tibia except for its proximal end, which is sharply bent backward. There are quantitative differences in these abnormalities, but the pattern is the same in all the abnormal young.

The microscopic changes of the abnormal skeleton have been studied in all the long bones of the extremities. They are rather uniform, and the deformed tibia, described in the next paragraph, can be considered a representative of the pathologic structures.

Comparison of a section of a normal tibia of a newborn rat (fig. 2 *A*) with that of a deformed specimen (fig. 2 *B*) shows that the latter is distinctly curved,

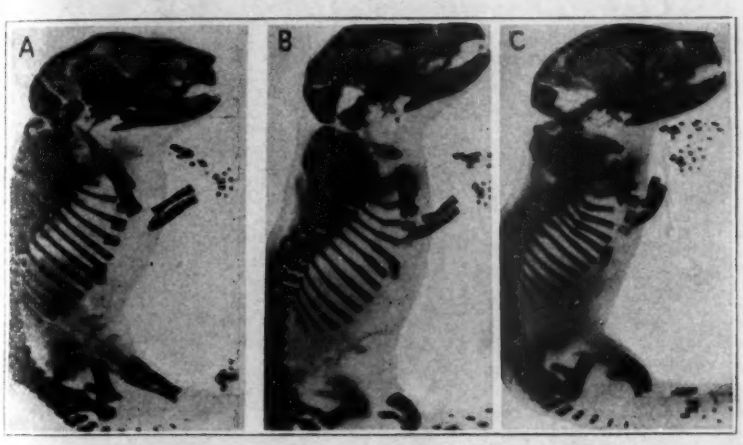

Fig. 1.—*A*, normal cleared newborn rat; *B* and *C*, abnormal cleared newborn rats showing curved radius, ulna, tibia and fibula. Note the broadening and angulation of the ribs (× 1.5).

with the convexity turned toward the anterior surface of the leg. Another obvious difference is found in the stage of ossification, which is much farther advanced in the normal than in the deformed tibia. In the latter the cartilaginous ends are of abnormal length and structure while the osseous shaft is reduced to about one fourth of its normal length. Both the resting cartilage and the columnar cartilage appear normal, but the area of swollen cartilage cells is much enlarged. Forty to sixty cells can be counted in the longitudinal direction as compared with eight to ten in the normal section. In preparations impregnated with silver, the intercellular substance in the zone of swollen cartilage is seen to be generally uncalcified. A few small areas situated immediately beneath the cortex and near the osseous shaft contain intercellular mineral deposits. The swollen cartilage cells remain unopened except for a small central zone in the long axis of the tibia (fig. 3). There a bush of capillaries protrudes into the cartilaginous mass. Osteoid tissue is present in this area but not so abundantly as in infantile rickets. Under the field of capillaries, calcified bone trabeculae can be discerned. The line of ossification is extremely irregular in these bones, since their osseous and cartilaginous parts are not sharply divided. Periosteal ossification is obviously more

nearly normal than the enchondral ossification. The cortical bone tissue envelops not only the osseous shaft but also the large areas of swollen cartilage. Thus the zone of swollen cartilage lies in a deep cup, the walls of which are formed by the cortical bone, while its base consists of the capillaries and osseous trabeculae of the shaft. The subperiosteal lamellas of the cortex consist of uncalcified osteoid tissue, while the deeper layers are made up of well calcified osseous lamellas.

Fig. 2.—*A*, section of a tibia of a normal newborn rat (× 21); *B*, section of a tibia of an abnormal newborn rat (× 22).

If viosterol is added to the maternal diet R, the changes described fail to develop in the young. Nineteen females bred while being fed diet R supplemented by 60 U. S. P. units of vitamin D every tenth day produced fifty-one litters, which consisted of 322 young. None of the cleared young showed the changes described in the offspring of mothers fed diet R without vitamin D. Vitamin D prevents the skeletal changes of the "pattern of diet R."

COMMENT

That the intrauterine development of the offspring of mammals is independent of the mother's diet is still a widely accepted thesis. Also it is often assumed that a lack of essential foodstuffs in the maternal diet results in fetal death and that nutritional conditions which permit normal termination of pregnancy assure

Fig. 3.—Axial section of the proximal end of a tibia of an abnormal newborn rat (× 115).

normal offspring.[11] Recent investigations have shown that this supposition is incorrect. There is evidence that deficiencies of vitamins or vitamin-like substances in the maternal diet can interfere with the normal development of the fetus

11. Needham, J.: Biochemistry and Morphogenesis, London, Cambridge University Press, 1942.

without interrupting its growth and viability.[12] In previous communications my colleagues and I have reported the appearance of skeletal abnormalities in the offspring of rats fed the Steenbock and Black diet 2965 supplemented with vitamin D (diet 1). A definite pattern of congenital malformations was described (pattern of diet 1).[13] These malformations were prevented when 2 per cent of dried pig liver was added to the maternal diet.

In the present report another type of congenital skeletal anomaly is described which can also be attributed to a deficient maternal diet. This diet—the Steenbock and Black diet 2965 supplemented with 2 per cent of dried pig liver (diet R)—is deficient in vitamin D and has an abnormally high calcium: phosphorus ratio. Since diet R is rachitogenic, one must consider the possibility that the skeletal changes in the young represent fetal rickets. The pronounced bowing of the long bones betrays the softness of these structures. The piling-up of swollen cartilage cells on the border of the epiphysis and shaft is also seen in rickets. However, the absence of large areas of osteoid tissue between this epiphysial cartilage and the osseous part of the shaft distinguishes the histologic picture described from that of infantile rickets.

It is obvious that the rachitogenic diet offered to the mother is not transmitted unchanged to the fetuses. They are nourished by nutritional elements transmitted through the placenta from the maternal blood stream. The final "fetal diet" is unknown. It should also be remembered that the reaction of cartilage and bone to a lack of vitamin D in fetal life may differ from that of the same tissues in postnatal life. Whether the skeletal changes described should be considered "fetal rickets" may be questioned. They are, however, closely linked with the vitamin D deficiency of the maternal diet R. This is demonstrated by the fact that supplementing diet R with vitamin D results in prevention of the deformities.

The changes produced in the young by the maternal diet R are distinctly different from those described as the "pattern of diet 1." There is no overlapping of the two patterns. They can be distinguished anatomically in the cleared specimens and histologically in representative sections.

The observations presented in this study add further proof to the thesis that maternal nutritional deficiency can result in deformities of the young. They also demonstrate that specific deficiencies result in specific malformations.

SUMMARY

Congenital skeletal malformations were observed in about 45 per cent of the offspring of female rats that were fed a rachitogenic diet.

Pronounced curving of the radius, ulna, tibia and fibula as well as angulation of the ribs occurred in the offspring.

Addition of vitamin D to the maternal diet prevented these malformations.

Children's Hospital, Cincinnati 29.

12. Hale, F.: The Relation of Vitamin A to Anophthalmos in Pigs, Am. J. Ophth. **18**: 1087, 1935. Warkany, J., and Nelson, R. C.: Appearance of Skeletal Abnormalities in the Offspring of Rats Reared on a Deficient Diet, Science **92**:383, 1940; Skeletal Abnormalities in the Offspring of Rats Reared on Deficient Diets, Anat. Rec. **79**:83, 1941.

13. Warkany, J., and Nelson, R. C.: Skeletal Abnormalities Induced in Rats by Maternal Nutritional Deficiency: Histologic Studies, Arch. Path. **34**:375 (Aug.) 1942.

Case Reports

METABOLISM OF BONE SALTS IN RESISTANT RICKETS

REPORT OF A CASE, WITH BALANCE AND RADIOACTIVE TRACER STUDIES

LIEUTENANT COMMANDER LEWIS GUNTHER (MC), U.S.N.R.
AND
ELMA T. COHN, PH.D.†

WALDO E. COHN, PH.D.
AND
DAVID M. GREENBERG, PH.D.
BERKELEY, CALIF.

Cases of rickets uncomplicated by renal disease which did not respond to the antirachitic treatment with ordinary doses of vitamin D have been reported by a number of investigators.[1]

Chemical balance studies of the bone salt metabolism have been carried out in a number of these cases.[1f, g] The changes in calcium and phosphorus metabolism have been reported to be not quite typical of ordinary infantile rickets but not at all like those of primary hyperparathyroidism. The urinary excretion of calcium has been reported to be above the level usually observed in active rickets. There is chemical evidence of a secondary hyperplasia of the parathyroids in this condition. Since hyperplasia of the parathyroids has been shown to be associated with rickets in experimental animals, this feature does not appear to be a unique characteristic of resistant rickets.

The use of induced radioactive isotopes of the biologically important mineral elements offers a new means of studying the fate of the bone salts in the animal organism. A number of such studies have been carried out on experimental animals.[2]

The present investigation is a report of the results of a study of the fate of labeled radioactive phosphorus and of the total calcium, magnesium and phosphorus balance in a case of intractable rickets.

REPORT OF CASE

A. S. was born May 13, 1926. The pregnancy was normal. The birth weight was 8 pounds 14 ounces (4,026 Gm.). He was breast fed and was normal for four months, at which time he refused the breast. After he was weaned, his appetite failed. Various formulas were tried, such as water, milk and dextrimaltose, Nestlé's lactogen, Mellin's food and protein milk.

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†Dr. Cohn died Sept. 15, 1941.

From the Division of Biochemistry, University of California Medical School.

1. (*a*) Bloomberg, M. W.: The Treatment of Persistent Rickets, Am. J. Dis. Child. **34**:624 (Oct.) 1927. (*b*) Gleich, M.: Arch. Pediat. **45**:504 (Aug.) 1928. (*c*) Shier, A., and Stern, A.: Arch. f. Kinderh. **78**:176, 1926. (*d*) Hess, J. H.: Rickets, Am. J. Dis. Child. **42**:488 (Aug.) 1931. (*e*) Shelling, D. H., and Hopper, K. B.: Calcium and Phosphorus Studies, ibid. **47**:61 (Jan.) 1934. (*f*) Highman, W. J., Jr., and Hamilton, B.: J. Pediat. **9**:56 (July) 1936. (*g*) Albright, F.; Butler, A. M., and Bloomberg, E.: Rickets Resistant to Vitamin D Therapy, Am. J. Dis. Child. **54**:529 (Sept.) 1937.

2. (*a*) Greenberg, D. M., in Luck, J. M.: Annual Review of Biochemistry, Stanford University, Calif., Annual Reviews, Inc., 1939, vol. 8, p. 269. (*b*) Cohn, W. E., and Greenberg, D. M.: J. Biol. Chem. **123**:185 (March) 1938.

Orange juice and cod liver oil (Mead's, U. S. P., N. N. R., 1926) were given in the supplementary formula at 6 weeks. The cod liver oil was not taken well at first, and another brand was substituted which was better tolerated (Kepler's, U. S. P., N. N. R., 1926).

Ultraviolet irradiation with a mercury vapor lamp was begun when the boy was 6 months of age and was used from Nov. 1, 1926 to July 15, 1927. During this period he was burned once. The ultraviolet irradiation was continued for five years. Calcium supplements were given in the form of tablets.

Administration of viosterol (irradiated ergosterol) in oil in doses of 20 to 30 drops was begun soon after the onset of his feeding troubles.

The first teeth erupted when the boy was 10 months old. He began to walk about the crib at the age of 1 year but did not walk alone until he was 16 months of age. In spite of the apparently adequate administration of cod liver oil and ultraviolet irradiation, a severe bilateral genu varum was noted at the age of 2 years. It affected the entire lower extremity, and with it was associated a coxa vara, with a consequent loss of abduction. The gait was waddling. At that time the roentgen changes seemed typical of rickets. Braces and manipulation in abduction were prescribed. A year later (1929), there was considerable improvement. There was less bowing, and the legs could be spread 22 inches (56 cm.).

In June 1929, when the boy was 3 years and 1 month old, his physician noted epiphysial enlargement of the wrists and hips. In December 1929 for the first time, small pockets of pus were noted in the lower and in the upper gums but they were unaccompanied by gingivitis. There was associated fever. The teeth which were extracted were normal.

On July 15, 1929, at 3 years and 2 months, osseous changes and mechanical deformities were still present. His physician began to doubt that he was dealing with a true picture of rickets. The patient was 30 pounds (13.6 Kg.) underweight, and a diagnosis of dyschondroplasia was suggested. However, consultation and a review of the roentgenograms reaffirmed the clinical diagnosis of rickets. In September 1930 another consultant raised the question of achondroplasia. Further roentgen study and review of the former roentgenograms by other consultants again produced the opinion that the changes shown in the roentgenograms were typically rachitic.

His measurements in January 1931 were: total height, 37½ inches (95 cm.); head to anterior spinous process, 19½ inches (49.5 cm.); anterior spinous process to ankle, 16¼ inches (41.3 cm.); head to groin, 23 inches (58.4 cm.); groin to sole, 14 inches (35.6 cm.); circumference of head, 21 inches (53.3 cm.); circumference of chest, 20 inches (50.8 cm.), and circumference of pelvis, 19 inches (48.3 cm.). For comparison, the mother's measurements were taken and were as follows: total height, 61¾ inches (156.8 cm.); head to the anterior spinous process, 28¼ inches (71.8 cm.) and anterior spinous process to ankle, 30¾ inches (78 cm.). The subsequent measurements gave practically the same ratio of length of leg to length of trunk.

In 1931 an analysis of the blood showed a calcium content of 12 mg. and a phosphorus content of 2.5 mg. per hundred cubic centimeters.

In March 1932 the patient was seen by another physician, who verified the diagnosis of rickets.

Since the appearance of pus about the gums in 1929, the patient had been subject to bouts of fever and oozing of pus from the gums, which necessitated the extraction of teeth. It was noted that a considerable number of the teeth were absent. Dental examination on April 5, 1932 showed: three permanent first molars erupted in excellent condition and the fourth permanent molar in process of eruption; two lower permanent incisors erupted in good condition, and two deciduous molars present, one of which had a small filling. The four upper incisors and the lower canine teeth, two upper deciduous molars and four lower deciduous molars had been extracted. All the teeth which had been extracted had been sound.

There were two other children, one fourteen months older and one two and one-half years younger than the patient. Both were in perfect health, and all three children were bright.

A review of the roentgenograms made at 3½ years showed active rickets. This is shown in figure 1. In March 1932, roentgen examination showed slight signs of healing at the epiphyses and severe osteoporosis (fig. 2).

On April 8, 1932, chemical tests yielded the following values (milligrams per hundred cubic centimeters of blood or serum): calcium, 10.4 (normal); inorganic serum phosphorus, 3.3 (below normal), and nonprotein nitrogen, 25 (normal). The carbon dioxide-combining power was 49 volumes per cent (normal). The urine was normal.

A general diet was prescribed on April 8, which included about 1 quart (950 cc.) of milk daily. Cod liver oil (10 D) was taken for about two weeks, when the patient contracted measles. When seen one month later, he was back on the regimen of 8 teaspoons of

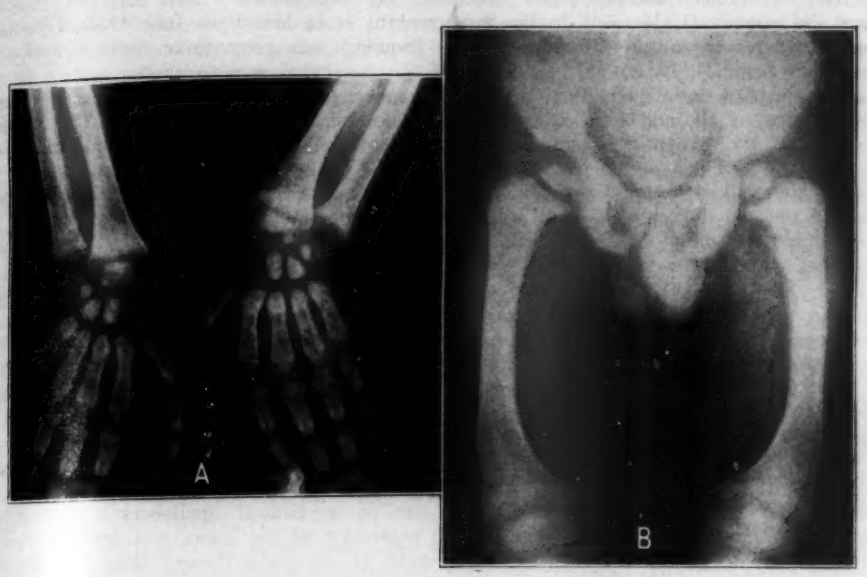

Fig. 1.—Roentgenograms showing active rickets. *A*, June 15, 1929; *B*, July 15, 1929.

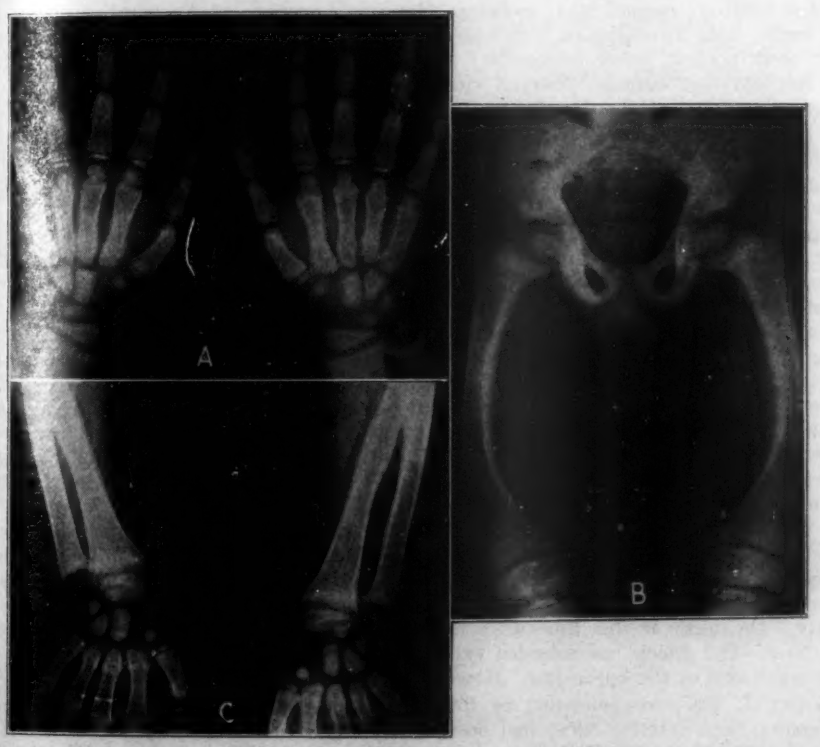

Fig. 2.—Roentgenograms showing evidences of healing while the patient was under the care of another physician. *A*, March 30, 1932; *B*, March 30, 1932; *C*, May 6, 1932.

cod liver oil (10 D) without added viosterol. He had grown 1 inch (2.5 cm.) and had gained 2½ pounds (1,134 Gm.) in the three months from March to June 1932. Five-tenths cubic centimeter of anterior pituitary extract (Squibb) was given three times a week from June 25 to Sept. 24, 1932.

Reexamination in September 1932 by the other physician showed another permanent incisor, three in all, and four first permanent molars. This physician gave the following statement of the patient's condition: He had grown ½ inch (1.3 cm.) and had gained 1¾ pounds (794 Gm.) in the preceding six months. He was bright, looked strong and was tanned. He walked better than before but still with a waddle. His appetite was poor. He liked the cod liver oil and was still getting 8 teaspoons daily. The intake of milk was 1 quart (950 cc.) daily. He slept well. He was 6 years of age; his height was 40¼ inches (102.2 cm.), and his weight was 40¾ pounds (18.5 Kg.).

From Sept. 24, 1932 until May 8, 1933, the patient was under the care of his own physician. During this period the intake of cod liver oil was reduced from 8 teaspoons to 1 teaspoon daily. The exact time when this reduction was made is not known, but it is thought to have been shortly before the child revisited the other physician for examination, on May 8, 1933. The physician's comments on this date were: "The patient has had a good winter. He is now receiving only 1 teaspoon of cod liver oil daily. His appetite has improved."

After this visit, the feeding of cod liver oil was discontinued. It was felt that the osteoporosis might be related to the continued large doses of cod liver oil and the doses of viosterol that had been administered. The use of mechanical appliances was continued, inasmuch as some bowing of the femurs, with separation of the knees, was present. A comparison of the length of the leg with the length of the body showed that the legs were growing in about the normal relation to the body.

In the summer of 1934, the family moved to Los Angeles, and the child was placed under the care of an orthopedist, who recorded the following observations on August 20: bilateral moderate anterolateral femoral bowing; bilateral enlargement of the femoral condyles and malleoli; normal hips; moderate Harrison's groove; no bleeding; moderate flaring costal angle; mild instability of both knees in anteroposterior and lateral positions; fontanels closed; teeth present, lower two molars and five cuspids, and upper two molars right, one molar left and four cuspids; pharynx clear except for some lymphoid tissue on both sides.

Roentgenograms of the femurs and the forearms submitted on April 3, 1934 showed severe femoral bowing with rotation, moderate coxa vera, flattening of the femoral heads and enlargement of the femoral condyles. They gave the appearance of juvenile rickets, although they were also extremely suggestive of dyschondroplasia. A diagnosis of delayed dentition and juvenile rickets was made.

Treatment consisted of brace adjustment and dietary measures, including the giving of orange juice twice daily. Administration of vitamin D was entirely discontinued. The orthopedist also felt that the osteoporosis was due to the excessive intake of vitamin D prescribed by the other physician during 1932.

In October 1934 the child had another acute illness marked by oral symptoms. Purulent material was oozing from the gums, and osteomalacia of the inferior mandible was suspected. The right lower first molar and the left lower central and the left deciduous cuspid were removed. Purulent material was found. When the pulp chambers of these teeth were opened, they showed purulent material. Cultures of the pulp of all the teeth produced Streptococcus viridans of the alpha type and Micrococcus pharyngis siccus. During a similar episode in January 1936, when an upper and a lower front tooth were removed, pus was also encountered in the nerve canal.

In June 1936 pus was again obtained, from a right second molar. The patient was given large doses of vitamin C and made an uneventful recovery. However, in September 1937 he had two more attacks of oozing gums with swelling of the soft tissues. Smears made from the pus grew Vincent's organisms. Neoarsphenamine (0.45 Gm.) was given intravenously. The teeth at this time were loose. The dose of the arsenical was repeated two weeks later. The attack had subsided except for a gumboil, from which pus was expressed, on the right side of the upper jaw. However, the teeth had become firm again.

On Oct. 7, 1937, reexamination by the orthopedist showed that growth was retarded in both femurs. The anterior curve had become strikingly corrected, although the lateral curve still persisted moderately. The femurs were 14¾ inches (37.5 cm.) long. His height was 4 feet ⅛ inch (122.2 cm.) and his weight 60.5 pounds (27.5 Kg.). The child had been in braces during this entire period, with periodic adjustments.

During this four year period, vitamin D therapy was not used, inasmuch as it was felt that the large doses of viosterol and cod liver oil previously administered were responsible

for the factor in the failure of healing of the rickets and the osteoporosis. During these four years, a number of episodes occurred as previously described of fever, swelling of the gums and oozing of pus from the gingiva. Repeated extractions were undertaken, and at all times teeth of normal structure were extracted. From February 1938 to November 1939, these bouts were controlled by the injection of neoarsphenamine in doses of from 0.15 to 0.45 Gm., but it did not entirely prevent the need for extractions.

One of us (L. G.) first saw the patient on March 21, 1938. The following observations were noted: He was small for his age, 11 years 10 months, his height being 48¼ inches (122.6 cm.). His general appearance was that of an achondroplastic child. His skull was long and narrow, with a large overhanging forehead. His thighs were strikingly bowed. His wrists were large. The angle of the chest was extremely wide. His arms and legs were short, and he walked with a pronounced waddle. He was unusually bright. His ears, nose and throat were normal. The lungs were clear and resonant. The heart was normal in size and shape, with rhythm regular and sounds of good muscular quality. The abdomen was soft. Results of a neurologic examination were normal.

The results of clinical laboratory tests were as follows:

April 19, 1939.—Hematologic Data: The hemoglobin content (Sahli) was 78 per cent (100 per cent, 17 Gm.). The red cells numbered 4,190,000 and the white cells 10,250, with 44 per cent polymorphonuclear leukocytes, 48 per cent lymphocytes, 2 per cent large monocytes and 6 per cent polymorphonuclear eosinophils. The mean corpuscular volume was 95, and the hematocrit reading (Wintrobe tube) was 38. The Wassermann reaction of the blood was negative.

The protein content of the serum was 5 per cent; the calcium content was 10 mg. and the inorganic phosphorus content 2 mg. per hundred cubic centimeters. The nonprotein nitrogen content was 35 mg. per hundred cubic centimeters of whole blood.

Urinary Data: The specific gravity of the urine was 1.026. Its reaction was acid, and it contained no sugar or albumin. Microscopic examination showed occasional white blood cells and epithelial cells, but casts were not noted.

The total volume of urine collected for the Addis count was 300 cc., and the specific gravity was 1.030. There were 5,000 white blood cells, no red blood cells and 2,500 hyaline casts. These results were interpreted as indicating normal urinary sediment, with no morphologic evidence of renal disease.

In the phenolsulfonphthalein excretion test 60 per cent of the amount of phenolsulfonphthalein injected intravenously was excreted in the first half-hour specimen and 24 per cent was excreted in the second half-hour specimen, a total of 84 per cent excreted in the first hour.

July 2, 1938.—Analysis of Stool for Fat: A twenty-four hour specimen of stool taken while the boy was partaking of a normal diet was analyzed for fat. The total weight of the stool was 605.9 Gm., and the total weight of the fat was 7.99 Gm.

Oct. 7, 1938.—Dextrose Tolerance Test: A test of the boy's tolerance for dextrose gave the following results: fasting sugar level, 62.5 mg. per hundred cubic centimeters of whole blood; level one-half hour after ingestion of dextrose, 106 mg.; one hour after ingestion, 155 mg.; two hours after ingestion, 62.5 mg., and three hours after ingestion, 64.5 mg.

Oct. 8, 1938.—Analysis of Gastric Contents: An analysis of the gastric contents after ingestion of an alcohol meal (100 cc. of 7 per cent alcohol) yielded the following data:

	Hydrochloric Acid	
	Free	Total
Fasting	0	4
One-half hour	0	5
One hour	0	6
0.5 cc. of histamine injected	..	..
Twelve minutes	0	6
Thirty minutes	8	20

Lactic acid was present in all specimens.

Sept. 5, 1939.—A later analysis of gastric contents gave the following results:

	Hydrochloric Acid	
	Free	Total
Fasting	0	8
One-half hour	0	10
Three-fourths hour	0	Quantity not specified

Nov. 11, 1939.—Test of Basal Metabolism: Basal metabolism was tested with the Sanborn metabolism machine, and the following data were obtained: age, 13 years; height, 51 inches (130 cm.); weight, 71½ pounds (32.4 Kg.); room temperature, 20 C.; barometric pressure, 29.5; oxygen consumed in eight minutes, 176 cc.; correction for temperature, + 1 cc.; correction for barometric pressure, — 2 cc.; arithmetical correction, — 1 cc. The actual consumption of oxygen was therefore 175 cc. The normal value for his sex is 166 cc., and the correction for his age is + 9 cc. His basal metabolic rate based on the Sanborn tabulation is, accordingly, 0 per cent.

Course.—Roentgen examination at this time showed evidence of unhealed and active rickets (fig. 3). On June 1, 1939, a special fish oil of high potency was supplied by Mead Johnson and Company, of Evansville, Ind. It assayed at 122,000 U. S. P. units of vitamin D and 46,000 U. S. P. units of vitamin A per gram. It was given by mouth, 1 Gm. per day. The hematologic data during the course of the treatment are shown in table 1. Growth continued at a more

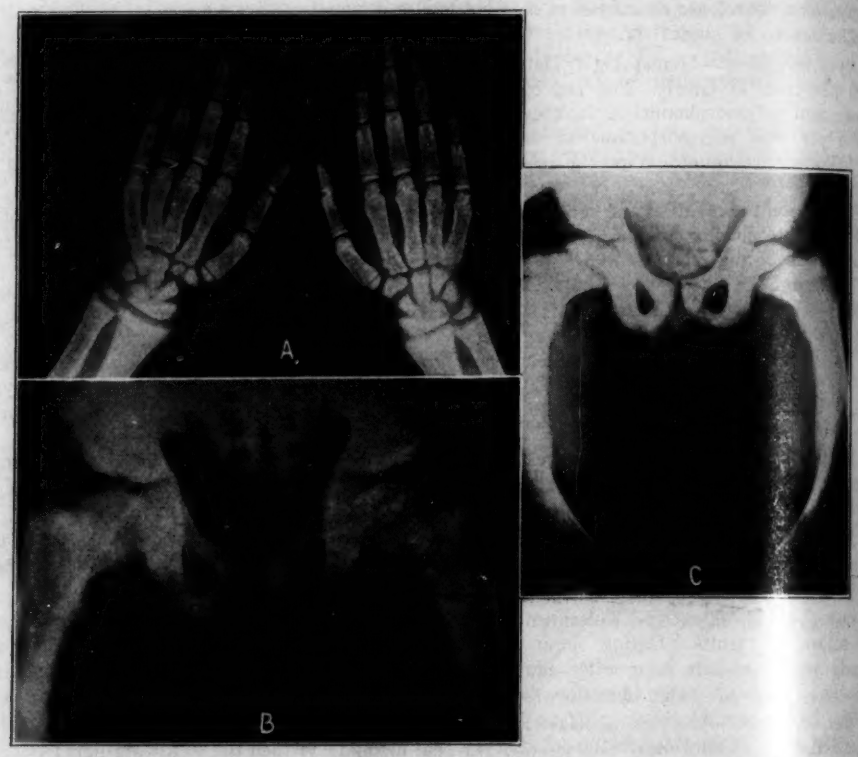

Fig. 3.—Roentgenograms at 13 years showing evidence of active rickets. *A*, taken by referring physician Feb. 9, 1938; *B*, taken at time of examination (April 21, 1938) by the senior author; *C*, taken April 25, 1938, showing rickets and marked osteoporosis.

rapid pace than before, and there was evidence of healing. The evidence of healing was complete by roentgen examination when operation to straighten the femurs was undertaken in 1941 (fig. 4, *A* and *B*). During 1940 the vitamin D intake was maintained at 50,000 units per day in the form of crystalline vitamin D. During the period while the boy was under treatment two teeth were extracted, and thereafter several other episodes of swelling of the gums occurred. There has been none since 1941.

BALANCE TRIALS

The balance experiments consisted of two three-day periods during which the patient received a diet high in calcium and two three-day periods during which he received a low calcium diet. The composition of the food was calculated from the tables of Sherman and checked by direct analysis of aliquot portions of each day's diet. The agreement between the calculated and the analyzed values was close.

In the analysis, the amount of calcium was estimated by the method of Larson and Greenberg [3]; of phosphorus, by the method of Fisk and Subbarow,[4] and of magnesium, by the method of Greenberg and Mackey.[5]

RESULTS

The agreement between the calculated and analyzed values for the calcium and phosphorus content of specimens of the food is shown in table 2. The results for the three day balance periods are recorded in table 3.

The results in table 3 show that a positive calcium and phosphorus balance can be maintained only with a high intake of calcium and phosphorus. With a low

TABLE 1.—*Chemical Changes in the Blood During Treatment with Oil of High Vitamin D Potency*

Date	Calcium, Mg. per 100 Cc.	Phosphorus, Mg. per 100 Cc.	Phosphatase, Units per 100 Cc.	Protein, Gm. per 100 Cc.	Comment
6/23/38	10.0	2.0	...	5.1	
7/ 6/38	10.0	2.7	...	7.0	
7/11/38	....	...	7.8	...	
11/21/38	11.2	2.6	9.8	7.7	
11/30/38	10.0	2.2	...	5.3	
12/ 1/38	....	...	11.5	...	
3/ 6/39	11.0	1.9	...	7.2	High phosphorus, normal diet
3/24/39	9.9	1.6	...	5.9	
4/ 6/39	10.0	1.2	...	8.2	Low phosphorus (0.5 Gm.) high calcium diet
4/12/39	9.9	1.8	...	6.0	
4/19/39	11.0	1.5	...	6.0	
4/26/39	11.0	1.4	...	7.2	
5/ 3/39	10.0	2.9	...	5.8	Vitamin D, 122,000 units
5/10/39	10.9	2.0	...	6.6	
5/17/39	10.6	1.7	...	6.4	
5/26/39	10.0	...	...	6.8	
6/ 1/39	....	1.8	...	6.0	Plus sunshine at camp
6/ 7/39	10.5	2.9	8.8	6.8	
6/15/39	10.0	2.5	11.6	...	
6/21/39	11.2	4.4	6.6	...	
6/27/39	10.2	4.9	2.8	...	
7/ 5/39	8.4	3.0	8.4	...	
7/11/39	11.3	7.6	5.6	...	
7/18/39	11.2	7.3	6.2	...	
7/26/39	11.5	8.4	7.7	...	Oil stopped
7/28/39	11.5	8.4	7.7	...	
8/ 9/39	10.2	4.5	13.0	5.8	
8/16/39	9.8	4.4	16.8	4.4	Vitamin D, 55,000 units
8/22/39	12.0	4.2	18.3	...	
8/29/39	10.6	3.2	18.3	...	Vitamin D, 92,600 units
9/ 5/39	9.4	2.7	22.8	...	Vitamin D, 122,000 units
9/20/39	11.5	3.0	19.8	6.0	
9/27/39	11.6	3.6	20.0	6.8	
10/ 4/39	10.4	3.1	9.2	6.0	Vitamin D
10/10/39	12.0	3.0	6.9	6.3	
10/18/39	12.4	2.9	10.0	5.6	Vitamin D, 185,000 units
10/21/39	12.0	2.8	10.0	...	Oil stopped
10/24/39	11.2	2.4	14.4	...	Vitamin D, 122,000 units
10/31/39	11.0	2.4	10.1	6.0	
11/21/39	11.2	2.6	9.8	7.7	

intake of calcium, the balances of both calcium and phosphorus become negative. Furthermore, the shifts correspond to the changes in the amount excreted in the feces. The urinary excretion of calcium and phosphorus remains relatively constant, in spite of the great changes in the calcium and phosphorus intake between the high and the low calcium diets. With regard to the urinary excretion of calcium, the data agree closely with those published by Albright, Butler and Bloomberg.

The results of table 3 lead to the inference that the primary factor at fault in the condition of resistant rickets is a failure to absorb calcium and phosphorus from

3. Larson, C. E., and Greenberg, D. M.: J. Biol. Chem. **123**:199 (March) 1938.
4. Fisk, C. H., and Subbarow, Y.: J. Biol. Chem. **66**:375 (Dec.) 1925.
5. Greenberg, D. M., and Mackey, M. A.: J. Biol. Chem. **96**:419 (May) 1932.

the food. To verify this inference for phosphorus, experiments were carried out with labeled radioactive phosphorus.

TRACER STUDY WITH RADIOACTIVE PHOSPHORUS

Radioactive phosphorus (P^{32}), prepared in the cyclotron of the radiation laboratory of the University of California, was converted into disodium acid phosphate (Na_2HPO_4) and administered in a small volume of water by mouth. The labeled

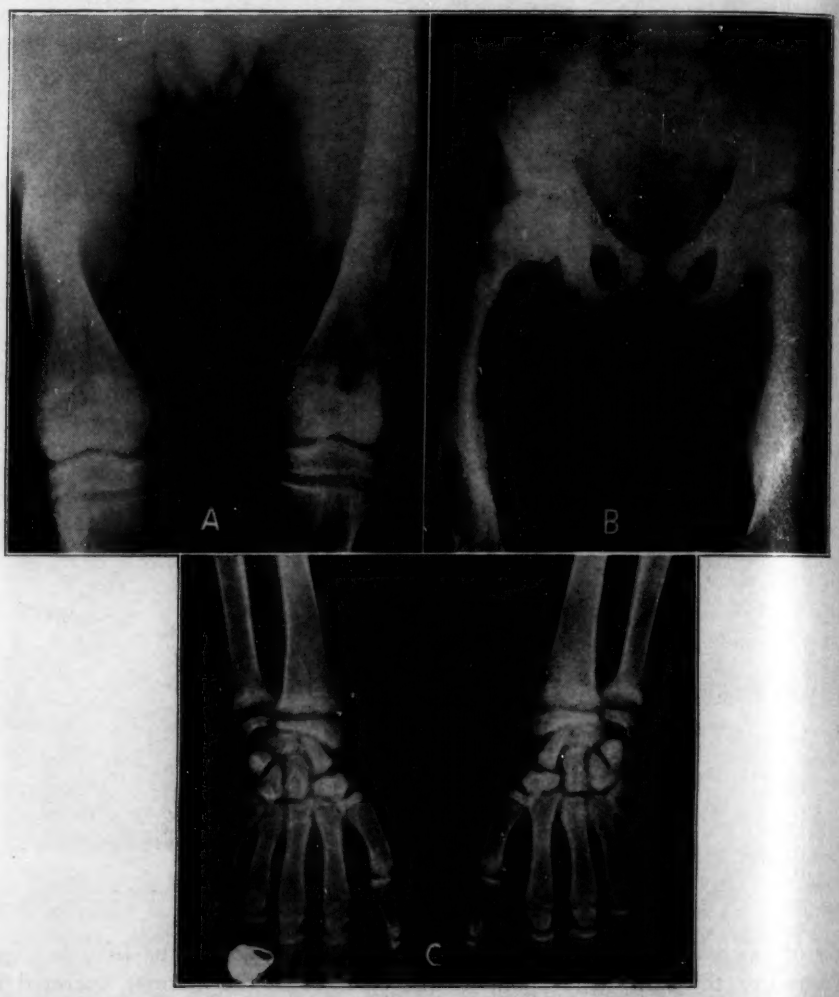

Fig. 4.—Roentgenograms showing healing and recalcification of bones. *A* and *B*, results of operative procedure to straighten the legs (compare with figure 3 *C*); *C*, healing of rickets.

samples contained only a few milligrams each of phosphorus, and the activity of the radioactive phosphorus was about 30 microcuries.

Urine and feces were collected continually for a week after the administration. The radioactive phosphorus content of each sample was measured, after ashing, with a Lauritsen electroscope and the results calculated in terms of percentage of the total dose. Analysis of total phosphorus was also carried out on each sample and the results used to calculate the ratio of labeled to unlabeled phosphorus.

The curves of excretion of the labeled phosphorus in the two trials are plotted in figure 5.

In experiment 1, the solution containing labeled phosphorus was given to the patient while he was in the postabsorptive state. The results of this test showed that there was practically complete absorption of the administered phosphorus. It had been planned to administer the second dose by injection, but since the first trial indicated this to be unnecessary the second dose was administered by mouth with food about two and one-half months after the first trial. In the first experi-

TABLE 2.—*Calculated and Analyzed Calcium and Phosphorus Composition of Specimens of Food*

Specimen	Calcium, Gm. per 100 Gm. of Food		Phosphorus, Gm. per 100 Gm. of Food	
	Calculated	Analyzed	Calculated	Analyzed
1	0.149	0.147	0.218	0.197
2	0.164	0.166	0.166	0.173
3	0.126	0.122	0.154	0.149
4	0.087	0.088	0.132	0.135
5	0.129	0.124	0.185	0.189
6	0.161	0.153	0.179	0.184

TABLE 3.—*Mineral Balance in Resistant Rickets* *

Period †	Calcium, Gm. per Day			
	Intake	Output		Balance
		Urine	Feces	
I	1.304	0.018	1.35	+0.026
II	1.29	0.023	1.07	+0.200
III	0.127	0.015	0.227	—0.115
IV	0.126	0.017	0.165	—0.056
Period †	**Phosphorus, Gm. per Day**			
	Intake	Output		Balance
		Urine	Feces	
I	1.70	0.75	0.81	+0.14
II	1.49	0.74	0.68	+0.07
III	0.79	0.70	0.263	—0.17
IV	0.74	0.55	0.222	—0.03
Period †	**Magnesium, Gm. per Day**			
	Intake	Output		Balance
		Urine	Feces	
I	0.337	0.078	0.298	—0.4
II	0.321	0.075	0.192	+0.055
III	.....	0.070	0.134	.....
IV	.....	0.070	0.119	.....

* Balances were studied during periods of three days.
† During periods I and II the intake of calcium was high; during periods III and IV the intake of calcium was low.

ment there was an excretion of 19.6 per cent in the urine and only 4.56 per cent in the feces in the period of a week. In the first thirty-four hours the fecal excretion amounted to 2.17 per cent.

In the dose administered with food, the fecal excretion amounted to 28 per cent of the dose in a week, and 21.5 per cent of this was excreted in the first twenty-four hours. The urinary excretion was about 14 per cent in the interval of one week.

If it is assumed that absorption in the first trial was 100 per cent, then the amount not absorbed in the second trial was 28 — 4.5 per cent, or 23.5 per cent, of the administered dose. From this the urinary excretion in terms of the absorbed

phosphorus in the second trial is 14/0.765, or 18.3 per cent. This checks closely with the 19.6 per cent excretion in the urine found in the first trial.

The results of these experiments show that the presence of food resulted in a decreased absorption of administered phosphorus, probably through the formation of insoluble calcium phosphate. This deduction is supported by the ratios of radioactive to total phosphorus in the samples. These ratios are recorded in table 4.

The results of table 4 support the view that a considerably larger fraction of the administered phosphorus remained unabsorbed and was swept through the intestine when the phosphorus was administered with food than when administered while the subject was in the postabsorptive state. The ratios also indicate that the urinary excretion of phosphorus is proportional to the amount absorbed.

Table 4 shows that after the first considerable elimination of the excess in the administered phosphorus the quantity which is retained becomes even more

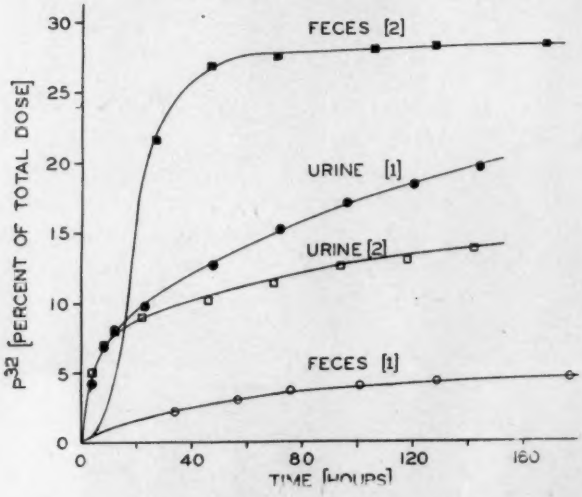

Fig. 5.—Excretion of labeled radioactive phosphate in a child with resistant rickets. Curves 1, dose of radioactive phosphate administered while the patient was in postabsorptive condition; curves 2, dose administered with food.

TABLE 4.—*Ratios of Radioactive to Total Phosphorus in the Excreta* *

	Feces Ratio × 100					
Hours After Administration	30	50	75	105	130	170
Experiment 1	0.30	0.20	0.075	0.055	0.050	0.033
Experiment 2	2.60	1.07	0.11	0.070	0.030	0.027

	Urine Ratio × 100								
Hours After Administration	4	8	12	28	48	72	96	120	144
Experiment 1	4.57	2.46	1.06	0.67	0.40	0.29	0.27	0.20	0.18
Experiment 2	3.40	1.65	0.84	0.52	0.37	0.21	0.14	....	0.13

* The ratio represents the percentage of the total number of milligrams of administered radioactive phosphorus in each sample of excreta divided by the total number of milligrams of phosphorus in the sample.

intimately mixed with the total phosphorus of the body and is only slowly eliminated as part of the regular catabolism of the body phosphorus.

The tracer experiments with labeled phosphorus lend no support to the hypothesis that the absorption of phosphorus, in any event, is a limiting factor in determining the healing or nonhealing of this type of rickets. This is in agreement with the results of experiments on rachitic rats.[6] Absorption of calcium may perhaps be the limiting factor; nothing in the present experiments either confirms or refutes this.

However, rickets, at least in the rat, is primarily a disease of phosphorus deficiency. If this is true in human rickets, including resistant rickets (and the low blood level of inorganic phosphorus favors this view), there is a strong suggestion that the primary defect in this disease is not in the absorption of the bone salts but rather in a failure of the calcifying mechanism.

SUMMARY AND CONCLUSIONS

A case is reported of resistant rickets in a boy who suffered from rickets from infancy until 14 years of age in spite of treatment with vitamin D and supplements of calcium salts. The disorder was corrected by the daily administration of fish liver oil high in vitamin D. The dose started at the level of 122,000 U. S. P. units per day and was eventually reduced to about 50,000 U. S. P. units per day.

Studies of mineral metabolism showed that a positive calcium and phosphorus balance could be maintained only when the intake of these elements was high. Otherwise both the calcium and phosphorus balances were negative. The changes in the balances corresponded to changes in the amounts of the minerals excreted in the feces. The urinary excretion of both calcium and phosphorus remained practically unchanged with either high or low calcium diets.

Tracer experiments with radioactive phosphorus showed that phosphate was readily absorbed from the intestinal tract by the patient. The hypothesis is offered that the primary defect in this condition is not failure of absorption of the bone salts but rather lies in a failure of the calcifying mechanism.

Dr. Charles S. Capp (M.D.), of the University of California Medical School Department of Radiology, gave helpful advice and interpreted the long series of roentgenograms.

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ACUTE GLOMERULONEPHRITIS OCCURRING IN THREE CHILDREN IN THE SAME FAMILY

RICHARD B. TUDOR, M.D.
Assistant Resident in Pediatrics, Bellevue Hospital
NEW YORK

Acute glomerulonephritis in siblings has rarely been reported,[1] which is rather surprising in view of the high incidence of infections of the upper respiratory tract and particularly in view of the known contagiousness of these infections. Hayman and Martin found that infections of the upper respiratory tract, including scarlet fever, preceded the onset of acute nephritis in 69 per cent of 976 cases which they studied.[2]

Löhlein, in 1907, was the first to furnish evidence to show that acute glomerulonephritis most often followed streptococcic infections.[3] Since then others have substantiated his observations concerning the etiologic role of the streptococci.[4] Sensitivity to bacterial products may also be a factor in the production of nephritis.[5]

The interval between the onset of the causative infection and the appearance of symptoms of nephritis varies from two days to four weeks.[6] If the onset is sudden, i. e. if a definite infection is known to precede the onset of nephritis, the prognosis is better than if the symptoms develop insidiously. The severity of the acute attack is not of importance.[6a] In Longcope's series of 141 patients, the nephritis commenced with an acute onset in 87.5 per cent and insidiously in 12.5 per cent.[6a] The mortality rate of acute nephritis usually averages 5 per cent to 9 per cent.[2] There is a great disagreement as regards the final outcome, however. Longcope, Murphy and Peters stated the belief that the recovery rate is 60 to 75 per cent,[7] whereas other observers set it between 80 and 90 per cent.[8] The

From the Department of Pediatrics, Duke University School of Medicine and Duke Hospital.

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2. Hayman, J. M., Jr., and Martin, J. W., Jr.: Acute Nephritis, Am. J. M. Sc. **200**:505 (Oct.) 1940.

3. Löhlein, M.: Ueber die entzündlichen Veränderungen der Glomeruli der menschlichen Nieren and ihre Bedeutung für die Nephritis, Leipzig, S. Hirzel, 1907; cited by Williams, R. H.; Longcope, W. T., and Janeway, C. A.: The Use of Sulfanilamide in the Treatment of Acute Glomerular Nephritis, Am. J. M. Sc. **203**:157 (Feb.) 1942.

4. (*a*) Bell, E. T.: Textbook of Pathology, Philadelphia, Lea & Febiger, 1938. (*b*) Snoke, A. W.: Stages, Prognosis and Duration of Glomerular Nephritis in Childhood, Am. J. Dis. Child. **53**:673 (March) 1937. (*c*) Longcope, W. T.: The Pathogenesis of Glomerular Nephritis, Bull. Johns Hopkins Hosp. **45**:335 (Dec.) 1929.

5. Schick, B.: Die Nachkrankheiten des Scharlach, Jahrb. f. Kinderh. **65**:132, 1907; cited by Rinkoff, S. S.; Stern, A., and Schumer, H.: Familial Nephritis, J. A. M. A. **113**: 661 (Aug. 19) 1939. Longcope.[4c]

6. (*a*) Longcope, W. T.: Some Observations on Course and Outcome of Hemorrhagic Nephritis, Internat. Clin. **1**:1 (March) 1938. (*b*) Bell.[4a] (*c*) Longcope.[4c]

7. Murphy, F. D., and Peters, B. J.: Treatment of Acute Nephritis, J. A. M. A. **118**:183 (Jan. 17) 1942. Longcope.[4c]

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failure of healing to develop within one year is of great importance in the prognosis.[9]

This report is based on a study of four brothers and sisters: John, aged 4 years, Marvin and Margaret, twins aged 3 years, and Mary, aged 5 years. They were of the white race. Nephritis developed in the three youngest children but not in the oldest child.

REPORT OF CASES

CASE 1.—Margaret, 3 years of age, had a mild infection of the upper respiratory tract for three weeks before coming to the clinic. When first seen, she had an infection of the upper respiratory tract, greatly enlarged and injected tonsils and bilateral cervical adenitis. Her temperature, pulse, respiratory rate and blood pressure were normal. Her urine had a trace of albumin and 4 to 6 red blood cells per high power field. She returned to the hospital three days later and was admitted. Abnormal physical conditions were: temperature 39.1 C. (102.4 F.), pulse rate 120 and blood pressure 110 systolic and 75 diastolic. She was acutely ill; there was a small amount of periorbital edema, and her tonsils were greatly enlarged and injected. She had a red blood cell count of 4,200,000, a white cell count of 12,600 and a hemoglobin content of 68 per cent. Her urine contained albumin (3 plus), many hyaline and granular casts and 5 to 10 red blood cells per high power field. The nonprotein nitrogen content of the blood was 75 mg. per hundred cubic centimeters. The content of total proteins was 6.2 Gm. per hundred cubic centimeters (albumin 3 Gm. and globulin 3.2 Gm.). The albumin-globulin ratio was 0.93.

CASE 2.—Marvin, 3 years old, became lethargic, and cervical adenitis, a swollen abdomen, periorbital edema, vomiting and reddish urine developed over a period of eleven days preceding his admission. His temperature was 37.2 C. (99 F); his pulse rate was 120 and his blood pressure was 135 systolic and 100 diastolic. He was acutely ill. There was a generalized edema, most marked periorbitally, and generalized lymphadenopathy and the tonsils were greatly enlarged and injected. A fluid wave was present in the abdomen, and the liver was felt 1 cm. below the right costal margin. He had a red blood cell count of 3,620,000, a white cell count of 14,800 and a hemoglobin content of 64 per cent. His urine contained albumin (3 plus), many hyaline and granular casts and many red blood cells per high power field. The nonprotein nitrogen content of the blood was 35 mg. per hundred cubic centimeters. The content of total proteins was 5.8 Gm. per hundred cubic centimeters (albumin 2.6 Gm. and globulin 3.2 Gm.). The albumin-globulin ratio was 0.81.

CASE 3.—John, aged 4 years, had a sore throat, cervical adenitis, fever and vomiting during a period of a week before his admission to the hospital. Physical examination revealed: temperature 37 C. (98.6 F.), pulse rate 84, and blood pressure 90 systolic and 58 diastolic. He was not acutely ill. There was no edema, but a generalized lymphadenopathy was present, and his tonsils were greatly enlarged and injected. He had a red blood cell count of 4,100,000, a white cell count of 18,600 and a hemoglobin content of 60 per cent. His urine gave a 3 plus reaction for albumin and contained many hyaline and cellular casts and 25 to 30 red blood cells per high power field. The nonprotein content was 79 mg. per hundred cubic centimeters of blood. The content of total proteins was 6.8 Gm. per hundred cubic centimeters (albumin 3.1 Gm. and globulin 3.7 Gm). The albumin-globulin ratio was 0.84.

CASE 4.—Mary, 5 years old, had an infection of the upper respiratory tract for one week before coming to the clinic. She was brought with her brothers and sister for a routine examination. Her physical condition was normal except that her tonsils were moderately enlarged and injected. Examination of her blood and urine gave normal results; therefore she was referred home. Nose drops and forced fluids were prescribed, and she was told to return to the hospital in a month. When she returned, she was in good health. She returned again eight months later and had her tonsils and adenoids removed; her brothers and sister had theirs removed at the same time. Her urine was always normal.

TREATMENT

On admission each child was given sulfadiazine in a dosage of 1 grain per pound (0.12 Gm. per kilogram) of body weight per twenty-four hours, one

9. Addis, T.: Hemorrhagic Bright's Disease, Bull. Johns Hopkins Hosp. **49**:203 (Oct.) 1931. Payne, W. W., and Illingworth, R. S.: Acute Nephritis in Childhood, Quart. J. Med. **9**:37 (Jan.) 1940. Hayman and Martin.[2]

half of the daily dose being given immediately. The use of sulfadiazine was continued until several days after the symptoms and signs of infection had ceased. Each child was also given 5 per cent solution of dextrose in distilled water intravenously several times and offered a liquid diet as desired. No attempt was made to restrict the intake of fluids. When a child refused fluids orally, his twenty-four hour fluid requirement was given to him parenterally. Magnesium sulfate was given both orally and intramuscularly if the systolic blood pressure was above 120 mm. of mercury, and its use was continued until the pressure had been normal for three days.[10] Cultures of materials from the nose and throat on admission contained many colonies of alpha and beta hemolytic streptococci in each plate. Vaccines made from these cultures were given subcutaneously to 2 of the children for eight months, three injections being given each week at first and then one each week. Each child responded well to the initial therapy and was discharged from the hospital at the end of three weeks. No differences were noted in the courses of the 3 children.

Subsequent Course.—Each child was seen in the outpatient clinic every two weeks after his discharge from the hospital. At each visit a complete history was taken and physical, blood chemistry and urinary examinations were done. One month after discharge no child had any blood or albumin in his urine, and all phenolsulfonphthalein tests showed normal excretion. Five months later the 4 children, including the oldest, who at no time showed any hematuria or albuminuria, were readmitted to the hospital for tonsillectomy and adenoidectomy. After these operations, from which they made rapid recoveries, they were discharged. All the urines were normal at this time. Although several attempts have been made to communicate with the family since that time, they have been unsuccessful.

CONCLUSION

In 4 children in one family, ranging in age from 3 to 5 years, infections of the upper respiratory tract developed which were followed in a few days by mild to severe signs of acute glomerulonephritis in 2 of them. The third child was found also to have nephritis by urinary examination and chemical studies of the blood. The fourth child did not have nephritis. Tonsillectomy and adenoidectomy were performed on all 4 children eight months after the initial infection of the upper respiratory tract and six months after the results of all blood and urinary examinations had become normal.

Routine urinalysis should be part of the physical examination of every ill child.

If all siblings of patients with acute glomerulonephritis had physical examinations plus examinations of the urine and determinations of blood chemistry, possibly a higher familial incidence of acute glomerulonephritis would be found.

Bellevue Hospital.

10. Thirty cubic centimeters of 50 per cent magnesium sulfate was given orally every four hours for moderate increases in the systolic blood pressure above 120 mm. of mercury. Five-tenths cubic centimeter per kilogram of body weight of 25 per cent magnesium sulfate was given intramuscularly for sudden pronounced rises of blood pressure and repeated in two hours if the pressure had not fallen to normal.

CHRONIC HYPERGALACTOSEMIA

FLOYD A. NORMAN, M.D.
AND
GLADYS J. FASHENA, M.D.
DALLAS, TEXAS

In 1935 Mason and Turner[1] reported a carefully studied case of prolonged galactosuria with associated nutritional and developmental disturbances in an infant. Theirs was the second case of such a condition to be described, the first having been reported by Göppert[2] in 1917. In both cases the outstanding clinical symptom was failure of the infant to gain and grow properly, and the chief abnormalities observed were enlargement of the liver and spleen and presence of galactose and albumin in the urine as long as the child received any considerable amount of milk. Both patients exhibited normal tolerance for dextrose and levulose but greatly decreased tolerance for lactose and galactose. Removal of milk from the diet resulted in remarkable improvement in both instances. Intensive study of the carbohydrate metabolism of their patient led Mason and Turner to postulate that galactose was apparently absorbed normally but failed to be converted to glycogen or dextrose at the normal rate. They suggested that the hepatomegaly was produced by excessive glycogen deposits formed from ingested dextrose under the stimulus of the artificially high level of total blood sugar induced by the galactemia. The pathogenesis of the condition was not clear. Their patient had suffered an attack of pneumonia at the age of 6 months which might have damaged the liver, while Göppert's patient had an enlarged liver at birth and shortly after birth severe icterus developed which lasted for eight months and which may well have been associated with hepatic damage. However, the rapid and striking regression of signs and symptoms following the elimination of milk from the diet makes it appear unlikely that acquired hepatic damage was responsible for the picture.

The purpose of this paper is to report another case of this abnormality of carbohydrate metabolism, with further carbohydrate studies. Our patient came under observation when younger than either of the patients in the previously reported cases and has been followed for two years.

REPORT OF A CASE

History.—R. W. C., a white boy, was born at term without difficulty on Jan. 17, 1941. The pregnancy had been uneventful, except for a threatened abortion during the eighth month, which was treated in the usual manner. His birth weight was 7 pounds 10 ounces (3,460 Gm.). Progress was apparently satisfactory for the first week of life, but when the child was 12 days old he began to vomit projectilely, usually after feeding although occasionally during feedings. This symptom persisted for approximately ten days, and he lost 16 ounces (454 Gm.). He was hospitalized in a local hospital and treated with hypodermoclyses and was given three intramuscular injections of blood and caroid (a digestent preparation of paparo) and bile salts

From the Children's Medical Center.

1. Mason, H. H., and Turner, M. E.: Chronic Galactemia: Report of Case with Studies on Carbohydrates, Am. J. Dis. Child. **50**:359 (Aug.) 1935.

2. Göppert, F.: Galaktosurie nach Milchzuckergabe bei angeborenem, familiärem, chronischem Leberleiden, Berl. klin. Wchnschr. **54**:473, 1917; cited by Mason and Turner.[1]

by mouth, which seemed to improve his condition slightly. Mellituria was observed on three occasions at the hospital. The child was discharged, without a definite diagnosis, on a cow's milk formula containing dextrimaltose. After a few days of fair progress the vomiting reappeared in nonprojectile form, and several changes of formula were instituted, without change in the infant's condition. At the age of 11 weeks he was referred to one of us (F. A. N.) and was admitted to the Children's Medical Center for study.

Family History.—The mother was 32 years old and in good health; the father was 34 years old and was also well. There was only one sibling, a girl of 5 years, who had always been well. There was no family history of diabetes, recent tuberculosis, allergy or cardiorenal disease.

Physical Examination.—The general appearance of the patient was that of a poorly developed, poorly nourished white male infant, appearing chronically ill. The skin was loose, and there was little subcutaneous tissue. A few small, soft axillary and inguinal lymph nodes were felt. The other significant observations were limited to a slightly protuberant abdomen and a smooth, firm liver, which extended 3 cm. below the costal margin. The spleen and kidneys could not be felt. The child weighed 7 pounds 11 ounces (3,488 Gm.). The measurements were as follows: length, 21¼ inches (54 cm.); circumference of the head, 14½ inches (36.8 cm.), and circumference of the chest, 13½ inches (34.3 cm.).

Laboratory Data.—The child's blood count on admission to the hospital was as follows: hemoglobin content, 7.9 Gm. per hundred cubic centimeters; red cells, 2,650,000; white cells,

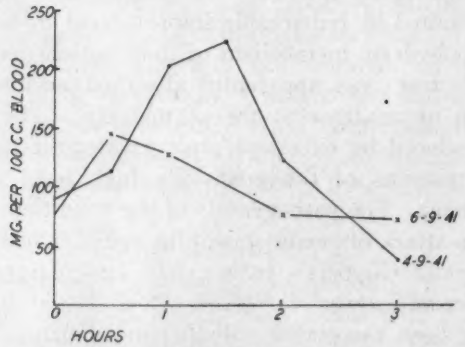

Chart 1.—Values for total blood sugar after ingestion of 1.75 Gm. of dextrose per kilogram of body weight on April 9 and June 6, 1941.

8,400; polymorphonuclear leukocytes, 27 per cent, of which 20 per cent were segmented and 7 per cent young forms; lymphocytes, 70 per cent; monocytes, 2 per cent, and eosinophils, 1 per cent. The Kline, Hinton and Wassermann tests on the blood gave negative results. The prothrombin time was within normal limits. Chemical analyses of the blood on admission gave the following results: urea nitrogen, 15.3 mg. per hundred cubic centimeters; total protein, 6.7 Gm. per hundred cubic centimeters, of which 4.7 Gm. was albumin and 2 Gm. globulin; fasting sugar, 105 mg., and cholesterol, 115 mg. per hundred cc. A bromsulphalein test, with 10 mg. of the dye injected intravenously, showed 20 per cent retention after thirty minutes.

Repeated examinations of the urine revealed the constant presence of a trace of albumin and a 2 to 3 plus reaction to Benedict's test. Ketone bodies were invariably absent. The urinary sediment always contained occasional finely granular casts and a few white cells but never any red cells.

On the day after his admission (April 9) a dextrose tolerance test was performed after a six hour fast. The values obtained are shown in chart 1. The fasting urinary sugar was 0.5 per cent; but in spite of the high blood sugar levels reached during the test, the subsequent urine specimens were free of sugar.

On his third day in the hospital, after a six hour fast, 30 Gm. of galactose was fed as a test of hepatic function, and for this reason only urinary sugar was determined. The fasting specimen showed 0.5 per cent, the two hour specimen 4.0 per cent and the four hour specimen 5.0 per cent of a reducing substance calculated as dextrose. Total excretion of sugar in four hours was 7 Gm. Twenty-four hours after the administration of the galactose the fasting blood sugar level was 97 mg. per hundred cubic centimeters, of which 47 mg. was nonfermentable

reducing substance.[3] Examination of the patient at this time revealed a perceptible increase in the size of the liver to a point 5 cm. below the costal margin. The tip of the spleen had also become palpable.

Urinary Data.—On the suspicion that we were dealing with a sugar other than dextrose, a twelve hour specimen of urine was subjected to chemical analysis after preliminary treatment with lead acetate followed by hydrogen sulfide to remove interfering substances. The results were as follows: By the Benedict copper reduction method 0.5 per cent of reducing substance (expressed as dextrose) was found. No reduction of Benedict's qualitative reagent occurred in the cold after twenty-four hours. Both Nylander's and Barfoed's tests elicited positive reactions. The Seliwanoff reaction was negative. The reducing power was unaffected by refluxing the acidified urine for ninety minutes. No decrease in reducing power was apparent after fermentation with an active suspension of washed yeast for two hours. After eighteen hours' fermentation, approximately 50 per cent of the reducing power was lost. The Tollens phloroglucin reaction gave a port wine color. A fine white alcohol-insoluble precipitate, considered to be mucic acid, was obtained after 50 cc. of urine had been acidified with 10 cc. of concentrated nitric acid, evaporated to 10 cc. and permitted to stand eighteen hours. An osazone prepared from the urine and recrystallized from acetone appeared identical with a similar preparation made from a 0.5 per cent solution of galactose. No determinations of melting point were made. Polariscopic examination of the cleared urine was carried out with use of a 1 decimeter tube and sodium light. A rotation of plus 0.38 degrees was observed. Using the usual formula and the specific rotation of galactose with sodium light as plus 81.5 degrees, we obtained a value of 0.47 per cent sugar, which agrees well with the percentage of sugar as determined by reduction of copper. From these data it appeared fairly certain that the reducing substance in the urine was galactose.

By the fifth day of hospitalization it became apparent that the condition of our patient closely resembled that of Mason's patient, and therefore the diet was changed to a soy bean milk substitute supplemented with ascorbic acid, thiamine hydrochloride and a cod liver oil concentrate. Three days after the dietary change a fasting blood sugar level of 102 mg. per hundred cubic centimeters was determined of which 23 mg. was nonfermentable.

Course in the Hospital.—After milk was eliminated from the diet, the infant improved remarkably. The vomiting ceased; the child began to take feedings eagerly, and his weight increased steadily more than 2 ounces (57 Gm.) per day. The liver decreased 2 cm. in size within a week. The urine became completely free of sugar the day after milk was eliminated and remained so. Albumin persisted in traces in the urine for a week and then disappeared. Occasional hyaline and finely granular casts were seen throughout the boy's stay in the hospital. Two transfusions of blood were given. On the twelfth day the patient was discharged on the soy bean formula supplemented with bone phosphate and vitamins and progressed favorably thereafter, without further untoward symptoms.

Second Admission to the Hospital.—On June 9, 1941, at the age of 5 months, the patient was again admitted to the Children's Medical Center solely for further study. In the interim he had grown at a normal rate and had gained 3 pounds (1,360.8 Gm.). On physical examination he appeared alert, active and happy. He had two lower central incisor teeth and showed moderate beading of the costochondral junctions. The abdomen was soft, but a firm, smooth liver could be felt 4 cm. below the costal margin. The spleen was not felt. The weight was 11 pounds, 4½ ounces (5,117 Gm.), and his measurements were: length, 23¼ inches (59 cm.); circumference of the head, 14 inches (35.6 cm.), and circumference of the chest, 16 inches (40.6 cm.).

The blood count on admission to the hospital was: hemoglobin content, 9.7 Gm. per hundred cubic centimeters; red cells, 3,800,000; white cells, 6,400; polymorphonuclear leukocytes, 16 per cent, of which 12 per cent were segmented and 4 per cent were band forms; lymphocytes, 80 per cent; monocytes, 3 per cent, and eosinophils, 1 per cent. The urine showed a faint trace of reducing substance but no albumin or ketone bodies. The microscopic examination showed a rare pus cell as the only abnormality. Results of carbohydrate studies carried out at this time are given in detail elsewhere in this paper. The urea nitrogen content of the

3. Total blood reducing substance was determined by the Folin-Wu macromethod. Nonfermentable reducing substance was determined by the same method on tungstic acid filtrates which had been fermented for one hour at 37 C. by a standard washed yeast suspension prepared according to Somogyi's method (Somogyi, M.: Reducing Non-Sugars and True Sugar in Human Blood, J. Biol. Chem. **75**:33 [Oct.] 1927). Complete fermentation of the dextrose present was assured by running parallel fermentation controls on other portions of filtrate to which pure dextrose had been added. Color comparisons were made in an Evelyn colorimeter against standards which differed from the unknown by not more than 5 mg. per hundred cubic centimeters in order to obviate proportionality error.

blood was 24.6 and 23.0 mg. per hundred cubic centimeters, respectively, on two occasions. A quantitative van den Bergh test of the blood serum by the method of Malloy and Evelyn [4] showed only a trace of color in the direct reaction and the equivalent of 0.2 mg. of bilirubin in the indirect reaction. Eight specimens of urine were analyzed for urobilinogen, and a trace was found only in one specimen. The total protein content of the serum was 6.4 Gm. per hundred cubic centimeters, of which 4.8 Gm. were albumin and 1.6 Gm. globulin. The serum calcium content was 10.4 mg. per hundred cubic centimeters; the inorganic phosphorus content, 4.7 mg., and the lipid phosphorus content, 8.3 mg. Roentgenograms of the long bones were reported to show some change in deposition of calcium suggestive of a metabolic disturbance but not characteristic of rickets.

Since the patient's tolerance toward galactose was found to be unimproved (see the section on carbohydrate studies) he was again discharged on the milk-free diet fortified with vitamins and bone phosphates. His subsequent course has been marked by a steady gain of weight, progressive decrease in the size of the liver and fairly normal development. At the age of 1 year he suffered a rather severe attack of pertussis, from which he recovered uneventfully. At 14 months of age he weighed 18 pounds 6 ounces (8,335 Gm.) and stood 28½ inches (72.4 cm.) tall. He walked well and had begun to talk. Bony and muscular development and dentition were normal. The edge of the liver could be felt at the costal margin, but the spleen was not palpable.

When seen at the age of 21 months the child's clinical progress continued to be satisfactory. At this time an early morning specimen of urine showed no albumin or reducing substance. Microscopic examination of the sediment showed no abnormalities. A Mosenthal test showed the ability to concentrate urine to a specific gravity of 1.037. The urea nitrogen content of the blood, however, was 23 mg. per hundred cubic centimeters, and a twenty minute bromsulfalein test using 2 mg. per kilogram of body weight showed no retention of the dye.

CARBOHYDRATE STUDIES

On the patient's second admission to the hospital the levels of the total blood sugar after ingestion of dextrose (1.75 Gm. per kilogram of body weight) were first determined. The dextrose tolerance curve was this time within normal limits (chart 1, June 9). A portion of the sample of blood taken at the height of the curve was fermented with washed yeast and was found to contain a nonfermentable fraction of 22.5 mg. per hundred cubic centimeters. This figure is not abnormally high for the method employed.[5] A comparison of this curve with the dextrose tolerance curve of April 9 (chart 1) reveals striking improvement in the patient's ability to handle ingested dextrose. The earlier curve was obtained while the patient's diet still contained cow's milk, during a period of severe derangement of the carbohydrate metabolism. The later curve was obtained after the patient had been on a milk-free diet for a period of several weeks. It is possible that the patient's poor tolerance for food in the earlier period resulted in relative carbohydrate starvation, which is known to produce dextrose tolerance curves of the diabetic type. It is more probable, however, that the high blood sugar levels in the first test represent some impairment in glycogenesis due to a large store of glycogen already present in the liver. Cori [6] has presented evidence suggesting that the store of glycogen in the liver limits the rate at which further glycogenesis can occur. We have observed a similar phenomenon in a case of von Gierke's disease.

It has been demonstrated that blood filtrates normally contain a nonfermentable reducing fraction composed chiefly of glutathione [5] and glucuronic acid [7] amounting to approximately 20 per cent of the total reducing action on the Folin-Wu copper reagent. It is conceivable that the abnormal increase in the nonfermentable frac-

4. Malloy, H. T., and Evelyn, K. A.: The Determination of Bilirubin with the Photoelectric Colorimeter, J. Biol. Chem. **119**:481 (July) 1937.

5. Fashena, G. J.: On the Nature of the Saccharoid Fraction of Human Blood, J. Biol. Chem. **100**:357 (March) 1933.

6. Cori, C.: Mammalian Carbohydrate Metabolism, Physiol. Rev. **11**:143 (April) 1931.

7. Fashena, G. J.: On the Nature of the Saccharoid Fraction of Human Blood: II. Identification of Glucuronic Acid, J. Biol. Chem. **137**:21 (Jan.) 1941.

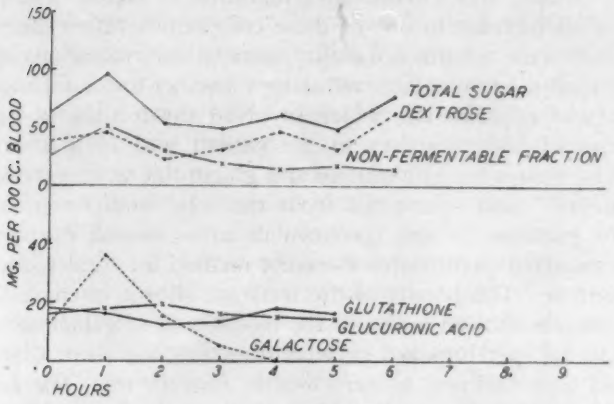

Chart 2.—Values for total blood sugar, dextrose and nonfermentable components obtained for a normal infant of the same age as the patient after ingestion of 1.75 Gm. of galactose per kilogram of body weight. Upper curves are expressed as milligrams of dextrose per hundred cubic centimeters of blood. Lower curves depict the components of the nonfermentable fraction. Values for glutathione and glucuronic acid are determined and expressed directly. Values for galactose are expressed in terms of reducing equivalents of dextrose. There was no excretion of sugar in the urine.

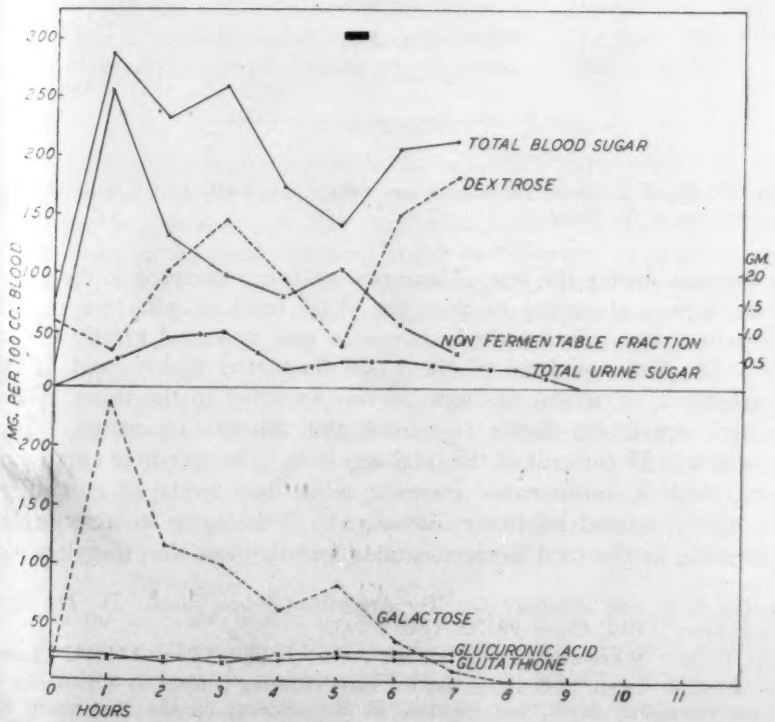

Chart 3.—Values for total blood sugar, dextrose and nonfermentable components obtained for the patient after ingestion of 1.75 Gm. of galactose per kilogram of body weight. Upper curves are expressed as milligrams of dextrose per hundred cubic centimeters of blood. Lower curves depict the components of the nonfermentable fraction. Values for glutathione and glucuronic acid are determined and expressed directly. Values for galactose are expressed in terms of reducing equivalents of dextrose. The total urinary excretion of sugar was 3.7 Gm. The blocked area represents a soy bean feeding.

tion observed by Mason and Turner after ingestion of lactose and galactose may have been due to an increase in one of these compounds rather than to galactose, as they inferred. To rule out this possibility, parallel determinations of glutathione,[8] glucuronic acid,[9] total nonfermentable reducing substance and total sugar were made in the next series of experiments, which involved the feeding of galactose (1.75 Gm. per kilogram of body weight) to the patient and to a normal control of the same age. The values for glutathione and glucuronic acid were translated into dextrose equivalents[10] and subtracted from the total nonfermentable fraction to obtain values for galactose. Each specimen of urine passed during the test was analyzed by the standard quantitative Benedict method for total reducing substance expressed as dextrose. The results of the tests are shown in charts 2 and 3. The normal control subject showed a rise in the blood level of galactose which reached a maximum of 36 mg. per hundred cubic centimeters one hour after the test dose was administered and declined to zero within four hours. The blood levels of dextrose, glutathione and glucuronic acid showed minor fluctuations but remained

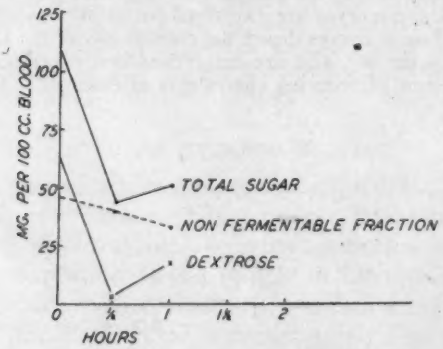

Chart 4.—Effect of 2.5 units of insulin on values for total sugar, dextrose and nonfermentable fraction of the blood.

relatively constant during the test. There was no sugar excreted in the urine. The patient's curve was abnormal in that the blood level of galactose rose to 240 mg. per hundred cubic centimeters in one hour and remained greatly elevated for six hours. The dextrose level of the blood fluctuated widely, and 3.7 Gm. of reducing substance calculated as dextrose was excreted in the urine. When Poe and Klemme's conversion factor[11] is used, this amount represents 5.3 Gm. of galactose, which is 53 per cent of the total ingested. The galactose curve paralleled that of the total nonfermentable fraction, while the levels of glutathione and glucuronic acid remained relatively unchanged. This leaves no reasonable doubt that the increase in the total nonfermentable fraction was due to galactose. It is

8. Benedict, S. R., and Gottschall, G.: The Analysis of Whole Blood: IV. The Determination of Glutathione, J. Biol. Chem. **99**:729 (Feb.) 1933.

9. Kapp, E. M.: Microestimation of Uronic Acids, J. Biol. Chem. **134**:143 (June) 1940.

10. One molecular weight of dextrose has the same reducing potency as 5 molecular weights of glutathione (Benedict, S. R., and Newton, E. B.: Studies on the Non-Sugar Reducing Substances of the Blood and Urine: I. Glutathione and Thionine in Blood, J. Biol. Chem. **83**: 361 [Aug.] 1929) and 1.5 molecular weights of glucuronic acid (Quick, A. J.: A Method for the Quantitative Detremination of Menthol Glucuronic Acid in Urine, ibid. **61**:667 [Oct.] 1924) toward the Folin-Wu copper reagent.

11. Poe, C. F., and Klemme, D.: Reducing Equivalents for Some Rare Sugars as Determined by Colorimetric Methods, J. Biol. Chem. **87**:7 (May) 1930.

noteworthy that the dextrose level of the blood fell to 32 and 35 mg. per hundred cubic centimeters on two occasions without overt signs of hypoglycemia.

In preparation for an insulin tolerance test, the patient's formula was changed to cow's milk fortified with 2 per cent lactose. He took three 5 ounce (150 cc.) feedings of this mixture eagerly but thereafter refused most of the formula and showed no evidence of being hungry. This constituted a striking contrast to his usual eager appetite when taking the soy bean formula and demonstrates the severe derangement which a small amount of lactose is evidently able to produce in a patient with this condition. On the following day 2.5 units of insulin (0.5 unit per kilogram of body weight) was administered after a forced feeding of 150 cc. of milk plus 3 Gm. of lactose (a total of about 10 Gm. of lactose). Water was offered freely throughout the test. The blood dextrose level dropped precipitously, with only a slight drop in the nonfermentable fraction (chart 4). In half an hour the total blood sugar was 40 mg. per hundred cubic centimeters, with a true dextrose level of 3 mg. At this point signs of insulin shock supervened, and although the level of total sugar and of true dextrose both rose slightly during the next half hour, the child lapsed into semicoma, which necessitated the termination of the test at one hour. Intravenous injection of a 50 per cent solution of dextrose produced rapid disappearance of all symptoms. This result is at variance with those of Mason and Turner, whose patient showed a rise in blood galactose and no signs of shock following administration of insulin although the blood dextrose level fell to 13 mg. per hundred cubic centimeters. It is possible that the amount of lactose given to our patient was insufficient to allow for a protective rise in blood galactose. This is unlikely, however, as the feeding given three hours before the test contained nearly 2 Gm. of lactose per kilogram of body weight.

COMMENT

Both the symptoms and the specific carbohydrate derangement of our patient parallel closely those in the previously reported cases of chronic galactemia. Ingestion of lactose or galactose not only produced a chronic galactosuria but exerted a profound effect on the child's general health as evidenced by intolerance for food, failure to gain weight, hepatomegaly, splenomegaly, secondary anemia and albuminuria. The mechanism of these widespread changes remains obscure. We believe that the primary difficulty lies in the inability of the patient to metabolize galactose normally and are inclined to agree with Mason and Turner's suggestion that the widespread systemic effects may be secondary to a continuously low level of dextrose in the blood. These workers adduced evidence suggesting that it is the height of the level of total blood sugar and not of that of dextrose alone which sets in motion the blood sugar–lowering mechanism. Since this mechanism cannot act efficiently on galactose in a patient with this condition, it acts excessively on dextrose, thus keeping the latter at an abnormally low level. Our results tend to bear out this hypothesis.

There is no evidence that this patient suffers from any of the usual forms of liver disease resulting in hepatic insufficiency. Bile pigment metabolism and bromsulphalein excretion have been entirely normal since milk was excluded from the diet. The reversible hepatomegaly appears to have been due to excessive storage of some metabolite, such as glycogen, fat or even galactose itself, in view of the observed large increase in the size of our patient's liver within twelve hours after the ingestion of 30 Gm. of galactose, with subsequent rapid decrease in size within a week of institution of a milk-free diet. The inconstant splenomegaly is more difficult to explain in this fashion, as carbohydrate is not ordinarily stored

by the reticuloendothelial system. Storage of lipid appears unlikely in view of the normal values for cholesterol and lipid phosphorus. As in the earlier cases, this patient had albumin in his urine as long as he excreted galactose in the urine. The albuminuria disappeared shortly after the galactosuria ceased. Here again the most likely explanation is the one presented by Mason and Turner, that disturbed dextrose metabolism caused imperfect function of the kidney cells. We have no explanation to offer for the continued low grade azotemia which our patient showed on three occasions after the galactosuria had ceased and all other symptoms had regressed.

The onset of symptoms at the age of 12 days without a history of antecedent illness in mother or child together with lack of evidence of organic hepatic disease once the patient was established on a milk-free regimen strongly suggests a congenital aberration in intermediary galactose metabolism analogous to that which exists in essential pentosuria and levulosuria. It appears likely that the specific enzyme system concerned with the conversion of galactose to glycogen is deranged.

SUMMARY

A third case of chronic hypergalactosemia associated with galactosuria, albuminuria, nutritional disturbance, hepatosplenomegaly, anemia, mild azotemia and osteoporosis is presented.

Removal of milk from the diet resulted in the disappearance of all symptoms except the mild azotemia.

It is suggested that the essential disturbance resides in the specific enzyme system concerned with the conversion of galactose to glycogen and that this constitutes an inborn error in metabolism.

The associated manifestations are interpreted as being the result of relative dextrose starvation.

2306 Welborn Street.

Progress in Pediatrics

CAUSES OF INFANTILE SUMMER DIARRHEA

ESTENIO HORMAECHE, M.D.

NORRIS L. SURRACO, M.D.

CIRO A. PELUFFO, M.D.
AND
PEDRO L. ALEPPO, M.D.
MONTEVIDEO, URUGUAY

THE IMPORTANCE OF SUMMER DIARRHEA AS A CAUSE OF INFANTILE MORTALITY

Situated between the thirtieth and the thirty-fifth parallel of latitude in the southern hemisphere, Uruguay is in the temperate zone, and its climate is comparable to that of the European shore of the Mediterranean. The incidence of various diseases is similar to that of other countries in the same latitude, and such diseases as malaria, yellow fever and typhus are not known to occur in this country. Infantile mortality in the first year of life is approximately 10 per cent, and this percentage is one of the lowest infantile mortality rates in South America. According to Schiaffino,[1] it decreased very little from 1895 to 1935—from 11 to 9 per cent. Bauzá,[2] comparing the number of deaths in 1926 and in 1935, found a mortality of 9.34 and 10.19 per cent, respectively, for those years. With a population estimated at 2,000,000 there are 42,000 births each year; therefore, in Uruguay there are annually 4,200 deaths of children under 1 year of age.

Analyzing the causes of this mortality, Bauzá arrived at the conclusion that deaths from gastrointestinal disorders, generally designated as diarrhea and enteritis, amounted to 1,176, or 28 per cent of the total number of deaths, in 1935. He stated further that in reality a high percentage of deaths which are registered as due to undetermined or insufficiently defined causes are to be attributed to diarrhea and enteritis and consequently that no less than 40 per cent of deaths of children under 1 year of age are of that origin. Thus, in Uruguay, there are annually a possible 1,680 deaths due to gastrointestinal diseases in children in that age group. Among infectious diseases in this country tuberculosis and diphtheria are considered as two major problems of medicosocial hygiene, as there were 2,825 deaths from tuberculosis and 395 from diphtheria in 1935. That year diphtheria was particularly widespread and severe. But, if one considers that these figures apply to the whole population, while mortality due to infantile diarrhea is considered only in children under 1 year of age, there is no doubt that at least in this country infantile diarrhea represents a problem of capital importance. Furthermore, in other South American countries infantile mortality as a whole, as well as mortality due to diarrhea, is two and even three times as high as in Uruguay.

The causation of infantile diarrhea has been attributed to numerous bacteria—Proteus (vulgaris, mirabilis and morgani), Pseudomonas aeruginosa, coliform

From the Institute of Hygiene of the School of Medicine of Montevideo, Dr. Arnoldo N. Berta, Director.

1. Schiaffino, R., in Informes sanitarios, Ministerio de Salud Pública, Montevideo, 1937, p. 1.
2. Bauzá, J. A., in Informes sanitarios, Ministerio de Salud Pública, Montevideo, 1937, p. 43.

bacteria and streptococci, among others. We have found all of these organisms frequently in normal stools as well as in stools of patients with diarrhea, and we think that the question of their importance in the causation of infantile diarrhea still remains open. Our work has been concerned only with the relation of Shigella and Salmonella to infantile diarrhea, since the pathogenicity of those genera for man has been proved beyond doubt. The extent of their participation in the causation of intestinal disorders has been variously estimated in the past, and, although it is quite possible that their prevalence is not the same in different countries, it seems probable that the differences observed are in part attributable to the different methods used in their isolation.

As long ago as 1902 and 1904, Flexner and his co-workers found that in 285 (69 per cent) of 412 cases infantile diarrhea was due to organisms now classified as belonging to the genus Shigella. This fact has been repeatedly confirmed in the United States, even though the figures there and in Uruguay are not in exact agreement. To mention only recent investigations, Cooper and associates [3] found in 1939 that in 102, or 49 per cent, of 209 cases studied in Cincinnati the infection was produced by Shigella, especially by the Flexner bacillus. Of the children under 1 year of age, 25 per cent had dysenteric infections, while of those above that age the number with these infections was 75 per cent. In Chile, Garcés [4] found in 1931 that in 51, or 47 per cent, of 108 cases the condition was produced by Shigella. In other countries, especially in Great Britain, Shigella infections seem not to be prevalent in diarrhea of children.

Although literature on "Salmonella food poisoning" in adults is extremely abundant, the available data on infantile salmonellosis are rather scarce and deal principally with sporadic cases. There is no doubt that the attention of medical authorities is attracted to Salmonella infection in human beings only by the occurrence of some outbreak of food poisoning, while sporadic cases of the infection in children are not carefully studied. We have found no references to systematic investigations on the presence of Salmonella in diarrhea of children or to the clinical course of such infection. Nevertheless, there can be hardly any doubt that it occurs frequently all over the world, as not only sporadic cases but outbreaks of the disease involving several children have been mentioned repeatedly by authors, such as Abramson, Frant and Oldenbusch,[5] Aballí and associates,[6] McKinlay [7] and ourselves.[8] Recently Ramón Guerra, Peluffo and Aleppo [9] reviewed the literature on extraenteric localizations of Salmonella infection in children, mentioning their own cases. Kristensen, Bojlén and Faarup [10] and Harhoff [11] pointed out that in Denmark Salmonella infections are more frequent in children than in adults.

"Epidemic diarrhea of the newborn" is frequently mentioned in the literature. Best [12] studied twenty-seven outbreaks of the disease in maternities in New York,

3. Cooper, M. L.; Furcolow, M. L.; Mitchell, A. G., and Cullen, G. E.: J. Pediat. **15**:172, 1939.

4. Garcés, C.: Rev. d. Inst. bact. **2**:45, 1931.

5. Abramson, H.; Frant, S., and Oldenbusch, C.: M. Clin. North America **23**:591, 1939.

6. Aballí, A., and others: Bol. Soc. cubana de pediat. **9**:123, 1937.

7. McKinlay, B.: Infectious Diarrhea in Newborn Caused by Unclassified Species of Salmonella, Am. J. Dis. Child. **54**:1252 (Dec.) 1937.

8. Hormaeche, E.; Peluffo, C. A., and Aleppo, P. L.: Arch. de pediat. de Uruguay **13**:368, 1942.

9. Ramón Guerra, A.; Peluffo, E., and Aleppo, P. L., in Bonaba and others.[14e]

10. Kristensen, M.; Bojlén, K., and Faarup, C.: Bibliot. f. læger. **129**:310, 1937.

11. Harhoff, cited by Kauffmann, F.: Die Bakteriologie der Salmonella-Gruppe, Copenhagen, Ejnar Munksgaard Forlag, 1941.

12. Best, W. H.: Epidemic Diarrhea of Newborn, J. A. M. A. **110**:1155 (April 9) 1938.

involving 750 among 5,082 newborn infants, with a fatality rate of 47.5 per cent. Frant and Abramson,[13] referring to this condition, stated that there had been an increase of such infections in nurseries in New York. The causative agent is unknown. Such outbreaks among newborn babies have never been reported in maternities in Montevideo, but it is impossible to say whether some of the infections which constitute our group of unknown causation are in reality "epidemic diarrhea of the newborn." It seems to us that the age of the children affected, the epidemic appearance and other characteristics of "newborn diarrhea" are not sufficient to distinguish this disease from Shigella and Salmonella infections in the newborn, which are not rare in this country and the occurrence of which in well defined outbreaks we have observed several times.

PERSONAL INVESTIGATIONS

In 1934 we undertook an investigation of the causation of diarrhea in children, which we have prosecuted since that time without interruption, using in our study principally patients with this disease admitted to children's hospitals in Montevideo. At the start our program was limited to bacteriologic examinations of the stools of children having enteritis in our search for dysentery bacilli and later for Salmonella.[14] We soon felt, though, the necessity of employing a group of controls, as we found the same bacteria in the stools of some infants with slight or no intestinal disorders as were found in stools of babies having diarrhea. Therefore, we decided to examine the stools of all children admitted, no matter for what cause. To detect extraenteric localizations of the same bacteria we performed many examinations of urine, pharyngeal exudate, pus from the middle ear and blood. Agglutination tests were done with serums taken from the patients, their own strains being used as antigens.

The present report covers our investigations during the six year period from June 1, 1936 to June 1, 1942. Our observations in previous cases were useful, since they familiarized us with the pathologic process of Shigella and Salmonella infections in children, but for statistical purposes they cannot be included, as the bacteriologic methods we were then using differed greatly from those we now employ.

All infections will be classified according to clinical features in two principal groups—those associated with and those not associated with enteritis. In the first group we include three distinct syndromes, which we call "dysenteriform," "choleriform" and "mixed." Under "dysenteriform" enteritis we include conditions showing the classic symptoms of bacillary dysentery, with its colic, "low" localization, its frequent passing of stools containing mucus, pus and often blood and its generally high temperature. By the "choleriform" syndrome we mean profuse, watery diarrhea and stools not showing blood or pus microscopically, corresponding to what is called "infantile cholera." Like true cholera, it is likely that this type corresponds to a localization in the small intestine, and some necropsies confirmed this view. As "mixed" enteritis we designate conditions which started as one of the two types just mentioned and subsequently evolved into the other.

13. Frant, S., and Abramson, H.: Am. J. Pub. Health **28**:36, 1938.

14. (*a*) Hormaeche, E., and Surraco, N.: An. Fac. de med. de Montevideo **23**:171, 1938. (*b*) Hormaeche, E.; Surraco, N., and Aleppo, P. L.: Arch. de pediat. d. Uruguay **10**:573, 1939. (*c*) Hormaeche, E.; Peluffo, C. A., and Aleppo, P. L.: Ztschr. f. Hyg. u. Infektionskr. **119**: 453, 1937; (*d*) Arch. de pediat. d. Uruguay **11**:8, 1940. (*e*) Bonaba, J., and others: Estudios sobre la etiologia infecciosa de las diarreas infantiles, Montevideo, Editorial Médica J. Garcia Morales, 1940. (*f*) Hormaeche, E., and Peluffo, C. A.: Puerto Rico J. Pub. Health & Trop. Med. **17**:99, 1941.

Under the common heading "not associated with enteritis" we include two groups of infections: (1) those without any intestinal disorder, which we call the intestinal carrier state; (2) those presenting only mild diarrhea, with slight or no repercussion on the general condition, in which stools number three to five a day and do not contain blood or pus but often contain mucus. These we call "plain diarrhea." The course of the disease is habitually benign, and the mortality is low.

We wish to emphasize that this classification, based only on clinical features, has no pretensions to accuracy. It seems obvious that in dysenteriform and in mixed enteritis there is present a localization of organisms in the intestine and that the name "enteritis" is justified; but in choleriform syndromes this is doubtful. Moreover, it must be said that in many cases classification is difficult, as the borderline between plain diarrhea and enteritis is rather indefinite, especially in infants under 1 year of age. In fact, it is highly probable that many disorders classified as plain diarrhea are only attenuated forms of enteric localizations of Shigella and Salmonella infection. Nevertheless, we believe that in any attempt to study diarrhea of children a previous classification of infections is indispensable, provisional and even inaccurate as it may be, provided the terms used are clearly defined.

By Shigella or Salmonella enteritis are meant infections in which we isolated one or the other of these bacteria from the stools of the patient. When culture of the stool was negative the data were not included in the statistics, even when, as happened several times, cultures of urine, pharyngeal exudate or blood were positive. We do not feel justified in attributing the causation of an intestinal process to a strain found elsewhere that is absent from the stools; however, it does not seem reasonable to include such enteritis in the same group with conditions which are classified as "of unknown origin," since the latter group contains only those with negative cultures.

When referring to "carriers" we mean persons that were considered as such because of the lack of intestinal disorders; many of them were not true carriers, as they had some extraintestinal localization of infection.

In some cases both Shigella and Salmonella were found in the stools. These were classified according to the results of agglutination tests performed with the patients' serums against the strains isolated. The bacterium for which specific agglutinins were found was considered as the causative agent, and when none were found the data of the case were not included in the statistics.

TYPES OF SHIGELLA AND SALMONELLA ISOLATED IN URUGUAY

During the six years mentioned, 3,592 children up to the age of 12 years were examined. The total number of bacteriologic examinations was 9,911, and for them about 120,000 isolation plates were used. We have already described in detail [15] the methods used for isolation and compared their respective values. The classification of the strains isolated was based on biochemical and serologic behavior. There were 891 positive cultures; in 393 Shigella was found, and 498 yielded Salmonella. In 34 of these patients one type of Shigella and one or more types of Salmonella occurred.

Types of Shigella.—From each of our 393 patients with dysentery we isolated one strain; there was never an association of different types of Shigella. They were classified as follows: Flexner, 327; Sonne, 35; Boyd's 88 (serologically the same as the Newcastle type of Warren and Scott), 22; Schmitz, 8; Boyd's P.143, 1. Not a single Shiga strain has ever been found in this country.

15. Hormaeche, E., and Surraco, N. L.: Arch. urug. de med., cir. y especialid. **18**:485, 1941.

Types of Salmonella.—We isolated 537 strains of Salmonella from 498 patients, not including strains found in adult patients during the same period. Their classification was as follows: S. typhi murium, 225; S. Newport, 124; S. Montevideo, 44; S. anatum, 23; S. Derby, 18; S. paratyphi B., 17; S. Bredeney, 13; S. cerro, 12; S. Oranienburg, 9; S. London, 6; S. Panama, 5; S. München, 5; S. meleagridis, 4; S. Chester, 4; S. cholerea suis var. Kunzendorf, 3; S. Give, 3; S. Nyborg, 3; S. arechavaleta, 3; S. Münster, S. Minnesota, S. Oregon, S. Newington and S. Senftenberg, 2 each; S. gaminara, S. Onderstepoort, S. carrau, S. St. Paul, S. narashino and S. Amersfoort, 1 each. Five of these types were first found and described by us in this country: namely, S. Montevideo, S. gaminara, S. carrau, S. cerro and S. arechavaleta. Great irregularities have been observed in the frequency with which the various types were isolated. As an example, we may mention that the eighteen strains of S. Derby were isolated during the years 1936 and 1937, and since that time not a single one has been found. Such types as S. Montevideo and S. anatum were isolated from cultures taken from children and flies during some periods but were not found again for months.

Mortality According to Age and Clinical Syndrome in Cases of Enteritis from June 1, 1936 to June 1, 1942

Ages	Dysenteriform			Mixed			Choleriform			Totals		
	Cases	Deaths	Mortality	Cases	Deaths	Mortality	Cases	Deaths	Mortality	Cases	Deaths	Mortality
1. Shigella enteritis												
0 to 1	90	34	37.77	12	7	58.33	7	7	100	109	48	44.03
1 to 2	60	11	18.33	9	4	44.44	3	3	100	72	18	25
2 to 12	71	4	5.63	5	1	20	3	0	...	79	5	6.32
2. Salmonella enterititis												
0 to 1	52	14	26.92	10	2	20	14	8	57.14	76	24	31.57
1 to 2	25	0	.....	8	3	37.50	7	2	28.57	40	5	12.50
2 to 12	27	0	.....	5	1	20	4	0	.....	36	1	2.77
3. Enteritis of Unknown Origin												
0 to 1	125	42	33.60	23	12	52.10	33	25	75.75	181	79	43.64
1 to 2	39	8	20.66	7	3	42.85	6	2	33.33	52	13	25
2 to 12	18	3	16.66	4	0	.....	1	0	.....	23	3	13.04

SHIGELLA AND SALMONELLA AS CAUSATIVE AGENTS OF INFANTILE SUMMER DIARRHEA

In studying infantile diarrhea we can use only 3,022 of our cases, as we have no information on the clinical course of the infections in the remaining 570. Of our 891 cases in which cultures were positive we can consider only 680, 304 in which Shigella and 376 in which Salmonella was found in the stools. The records of the remaining 211 cases in which cultures were positive include extraintestinal findings with negative cultures of stools as well as cases without clinical data.

SHIGELLA AND SALMONELLA AS CAUSES OF ENTERITIS

Of the total of 3,022 cases just mentioned, 668 were classified as cases of enteritis. In 260 (38.92 per cent) of these the infections were due to Shigella, in 152 (22.75 per cent) to Salmonella and in 256 (38.32 per cent) to an unknown causative agent. The table shows the distribution of these cases according to age of the patient and causation and clinical classification of the infection as well as their respective mortality.

According to the figures in the table, the dysenteriform syndrome is the one most frequently encountered in cases of infantile enteritis, regardless of the cause of the infection (85 per cent of cases of Shigella enteritis and 65 per cent of cases of

Salmonella enteritis). It is not possible to differentiate one of the etiologic groups from the others by clinical features. Choleriform enteritis was produced more frequently by Salmonella (in 16 per cent of the cases) than by Shigella (in 5 per cent of the cases). As regards mortality, choleriform enteritis was more severe than the other types, regardless of its causative agent; hence clinical classification is useful for prognosis. The age of children is an important factor in prognosis, since mortality decreases rapidly in children over 1 year and is extremely low in children between 2 and 5 years of age. No deaths occurred in 40 cases of enteritis in children from 5 to 12 years of age.

To obtain information concerning the relative frequency of Shigella and Salmonella as causative agents in enteritis of children, it is necessary, as the

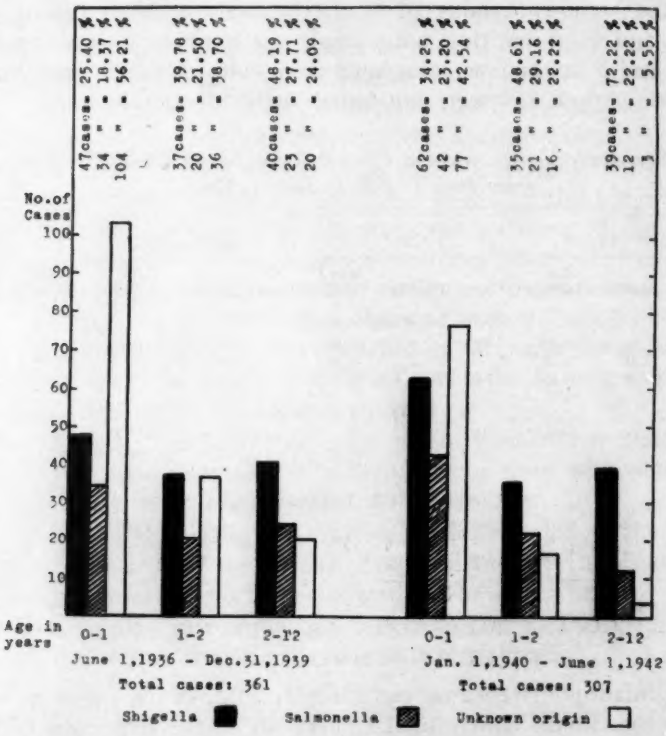

Chart 1.—Relative frequency of occurrence of Shigella and Salmonella as causative agents in enteritis in children according to ages.

bacteriologic methods used for diagnosis were different in the two periods, to divide our patients into two groups: those observed from June 1, 1936 to Dec. 31, 1939 and those observed from Jan. 1, 1940 to June 1, 1942. Up to January 1940 plates of lactose-litmus-agar were used for the isolation of Shigella. Since then we have used in addition "S. S." agar (prepared after the Difco Laboratories formula) and plates of Leifson's desoxycholate-citrate agar. As for Salmonella, we used Kristensen, Lester and Jürgens agar for isolation and Kauffmann's "K" tetrathionate for enrichment; but we added S. S. agar for isolation and a second medium for enrichment, Leifson's selenite "F." With the addition of these new mediums better results were obtained, so that the number of instances of enteritis of unknown origin has decreased considerably. In chart 1 are given 668 instances of enteritis that occurred in the two aforementioned periods.

It can be deduced from these figures that the occurrence of Shigella and Salmonella as causative agents in infantile enteritis, in absolute numbers, is in inverse proportion to age, a proof that children are more susceptible to infection with these organisms than adults; but if the percentages of such infections are considered in relation to the total incidence of enteritis, it is evident that they vary in direct proportion. In the first year of life 57.45 per cent of enteritis was of known origin; in the second year, 77.77 per cent, and between the second and the twelfth year, 94.44 per cent. These figures confirm the findings of Cooper and his co-workers in their investigation of dysentery. It follows that the problem of enteritis in children must be considered in terms of different ages and that in the study of its causation any comparisons drawn must be those made between groups of similar age. For children over 2 years of age one may say that the problem is practically solved, but in infants under 1 year 42 per cent of the infections were of unknown origin.

DISTRIBUTION OF ENTERITIS ACCORDING TO SEASONS

In chart 2 is given the seasonal distribution of 261 cases of enteritis studied from Feb. 1, 1940 to Feb. 1, 1942. Although only 261 cases are included in this table, seasonal distribution of this condition is exactly the same as in our total of 668 cases. We prefer to consider only the smaller number, since it is evident that among the infections which in the past were included in our group of unknown causation there were many infections caused by Shigella and Salmonella. It is clear that Shigella and Salmonella play an important part as causative factors in what is called "infantile summer diarrhea," although the distribution of these two conditions in relation to seasons is not exactly the same. Dysentery is most prevalent in Montevideo in December, corresponding to June of the northern hemisphere. As the mean temperature (chart 2) is higher in January and even in February than in December, as we have pointed out before,[14b] it can be deduced that ambient temperature is not the only factor influencing the occurrence of dysentery.

PLAIN DIARRHEA AND CARRIER STATE

The relative frequency of enteritis, plain diarrhea and the carrier state was different in Shigella and in Salmonella infections. For this comparison we can use 680 cases, 304 with Shigella and 376 with Salmonella found in the stools.

Shigella Infections.—These infections were divided as follows: enteritis, 260 (85.52 per cent); plain diarrhea, 38 (12.50 per cent), and carrier state, 6 (1.97 per cent).

Salmonella Infections.—These were classified as follows: enteritis, 152 (40.42 per cent); plain diarrhea, 190 (50.53 per cent), and carrier state, 34 (9.04 per cent). According to the ages of the patients the infections can be classified in the following way: in those 0 to 1 year, enteritis 76 (31.40 per cent), plain diarrhea 149 (61.57 per cent) and carrier state 17 (7.02 per cent); in those 1 to 2 years, enteritis 40 (51.28 per cent), plain diarrhea 31 (39.74 per cent) and carrier state 7 (8.97 per cent); in those 2 to 12 years, enteritis 36 (64.28 per cent), plain diarrhea 10 (17.84 per cent) and carrier state 10 (17.84 per cent).

Comment.—From a consideration of these figures it can apparently be deduced that Salmonella is less pathogenic for the human race than Shigella, as mild symptoms and the carrier state are found more frequently among Salmonella than among Shigella infections. We think, though, that this would be a rather rash assumption, as it has not been proved that the methods for the isolation of Shigella are as good as the ones available for isolation of Salmonella; and we have sound

reasons to believe that the contrary is true. Probably many instances of mild dysentery escape detection on account of the failure of methods of isolation.

It is interesting to note that in cases of infection caused by Salmonella plain diarrhea was relatively more frequent in infants under 1 year of age than in those above that age. The explanation of this fact is for the time being a matter of speculation.

MIXED INFECTIONS

We will mention separately cases in which Shigella and Salmonella were associated and those in which several types of Salmonella were found.

Association of Shigella and Salmonella.—We have observed 34 cases of these infections, divided into the following groups:

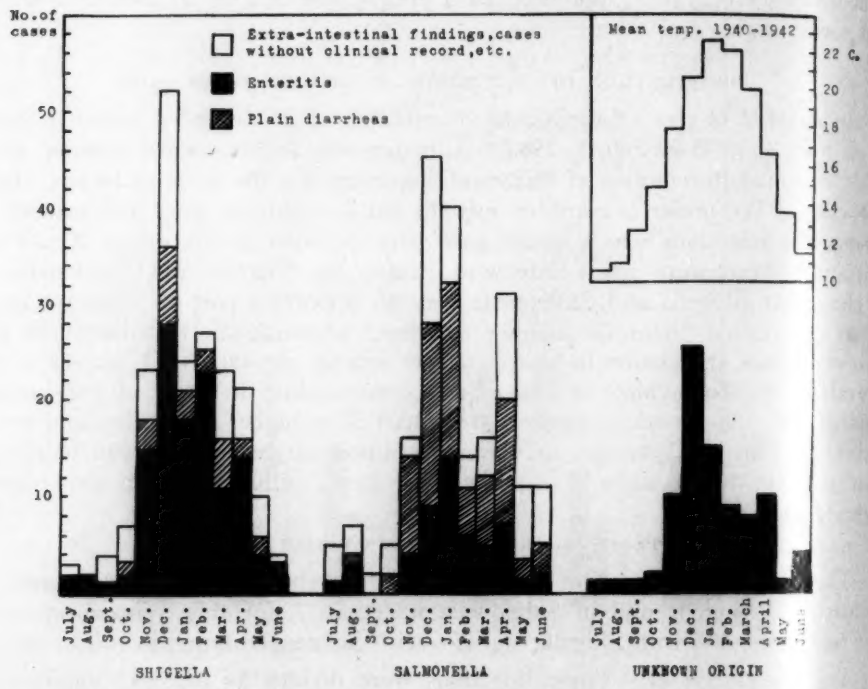

Chart 2.—Number of cases of enteritis, of plain diarrhea and of extraintestinal localizations of infections and of cases without clinical data from Feb. 1, 1940 to Feb. 1, 1942.

Shigella Enteritis (11 cases): In 10 cases Flexner bacilli and in 1 a Schmitz bacillus were found. In 10 of the cases we found both dysentery bacilli and Salmonella in the stools, and in 2 cases two types of Salmonella were found. In 1 case Salmonella was isolated from the urine and Shigella was found in the stools. In all these cases of enteritis agglutination reactions were positive for the isolated Shigella and negative for Salmonella.

Salmonella Enteritis (4 cases): In 2 of the 4 cases we found both Shigella (in 1 Flexner; in 1 Sonne) and Salmonella in the stools. In the third we isolated Salmonella from the stools and the Sonne bacillus from the pharyngeal exudate; in the fourth Salmonella was isolated from the stools and the Flexner bacillus from the urine. In these 4 cases a diagnosis of Salmonella enteritis was based also on agglutination tests, with positive reactions for Salmonella and negative reactions for Shigella.

Enteritis Without Diagnosis (11 cases): The reports of these 11 cases were eliminated from the statistics for lack of evidence as to the causation of the infections. Some of them were rather surprising. As an example, we shall mention the case of a boy of 2½ months with dysenteriform enteritis. A culture of the stool was negative; a culture of the blood yielded the Flexner bacillus, and from pharyngeal exudate S. senftenberg was isolated. Agglutination tests ten days after the onset gave negative reactions. Eight days later the Flexner bacillus was agglutinated in a dilution of 1 to 40, but agglutination tests with Salmonella gave negative results. The child recovered.

Plain Diarrhea (8 cases): In 4 of these cases we found both Salmonella and Shigella in the stools; agglutination tests gave negative results. In the fifth case we found S. Panama and S. typhi murium in the stools and the Flexner bacillus in the urine; agglutination tests were positive in a 1 to 80 dilution for the Flexner bacillus and negative for Salmonella. In the sixth case we found S. typhi murium in the blood three times and in the urine four times; from vaginal exudate we isolated the Flexner bacillus; a culture of the stool was negative. Agglutination tests were positive for the Flexner bacillus in a 1 to 40 dilution, and negative for Salmonella eight times. Clinically this was a case of septicemia, and the child recovered. In the seventh case we isolated S. typhi murium twice from the blood and once from pus from both ears and from the urine. The patient died with a septicemic syndrome, and we again isolated S. typhi murium from the blood, spleen, bone marrow and lung taken at autopsy; but we also found the Flexner bacillus in the lung. In the eighth patient, a child of 11 months, we found the Flexner bacillus in the stools and S. typhi murium in the blood; this was a fatal infection, the diagnosis of which was septicemia.

Infections Caused by Association of Several Types of Salmonella.—We have found 32 cases of associated infections—with two types, 28; with three, 2; with four, 1, and with five, 1. Recently we have mentioned some of these cases in detail.[14e] Lately we found another case in which we isolated ten different types of Salmonella on several examinations. The patient was a girl of 7 years with symptoms of food poisoning, from which she recovered.

Of the 32 patients, 13 had plain diarrhea and 9 enteritis caused by Salmonella. Four were intestinal carriers, and 2 had enteritis caused by Shigella, already mentioned. We have no information of the course of the infection in the remaining 4.

EXTRAINTESTINAL FINDINGS

As for extraintestinal localizations of infections caused by Shigella and Salmonella in children, the following data may be mentioned:

Shigella.—Sixty-three cultures of pharyngeal exudate were examined, of which 3 (4.76 per cent) were positive; 38 cultures of urine, of which 7 (18.42 per cent) were positive; 44 cultures of blood, of which 3 (6.81 per cent) were positive, and 19 cultures of pus from the middle ear, with none positive.

In 2 cases of vaginitis in small girls we isolated the Flexner bacillus from vaginal exudate. In 1 case, previously described, we isolated the same bacillus from the lung, and in another we isolated the Sonne bacillus from pharyngeal exudate.

Salmonella.—One hundred and fifty-seven cultures of pharyngeal exudate were examined, of which 16 (10.10 per cent) were positive; 123 cultures of urine, of which 40 (32.52 per cent) were positive; 174 cultures of blood, of which 18 (10.34 per cent) were positive, and 67 cultures of pus from the middle ear, of which 14 (20.89 per cent) were positive.

Extraintestinal findings were more frequent in Salmonella than in Shigella infections. The presence of Salmonella in pus from the middle ear, urine and pharyngeal exudate was relatively frequent and is worthy of note.

We have observed no relation between the severity of the intestinal syndrome and the extraenteric localizations, including invasion of the blood. Of our 18 patients with positive blood cultures, 8 had septicemia without any intestinal disorder; 4 had enteritis; 4 apparently had bacteremia in the course of plain diarrhea, terminating as septicemia, and 2 had bacteremia associated with enteritis. It should be mentioned that cultures of the stools of several of our patients with septicemia were constantly negative while cultures of pharyngeal exudate and of pus from the middle ear were repeatedly positive.

In typhoid-like types of Salmonella infections results of agglutination tests were generally positive, reaching flagellar titers of 1 to 1,280 and somatic titers of 1 to 320. In cases of plain diarrhea and enteritis they were also often positive, irrespective of the age of the child. As a rule, in infants under 1 year of age agglutinins appeared later than in adults, in general between ten and twenty days after the onset; they disappeared quickly, and between two and three months after recovery they were no longer present. Among extraintestinal localizations of Salmonella infection it is necessary to mention meningitis, of which we have described 2 fatal instances.

COMMENT

It is evident that at present it is impossible to establish exact figures concerning Shigella and Salmonella as causative agents of infantile diarrhea. There is no doubt that methods of isolation leave much to be desired, especially in the case of Shigella, as proved by the commonly observed fact that a positive result often is obtained only after one or several negative ones. The finding of Shigella in the urine and the blood of patients with dysenteriform enteritis while cultures of the stools were negative probably is attributable also to failure of methods of isolation. This is true even in the case of isolation of Salmonella, the bacteriologic methods for which are probably better but cannot be evaluated exactly.

Among the factors influencing results in diagnosis, early examination and reduction of the time elapsing between the passage of the stools and their examination are most important. In this respect we have worked at a disadvantage, as children usually are admitted to hospitals only several days after the onset of the disease and often only to die; there was an average lapse of eight hours before collected materials were examined. Also, in many cases it was possible to secure only one culture of the stools. For these reasons it is highly probable that the occurrence of Shigella and Salmonella in patients with infantile enteritis is greater than the 57 per cent which we found in all cases of this disease in infants under 1 year.

In cases of mixed infections it is sometimes impossible to decide the respective part played by each of the bacteria found in the stools or elsewhere, and we can offer no explanation for the amazing fact that sometimes we isolated five and even ten different types of Salmonella from the same child. We believe, though, that such occurrences are more frequent than is generally thought. We are convinced that the routine requirement in this laboratory that no fewer than forty colonies from each patient are to be fully classified and that all colonies on a plate are not to be accepted as belonging to the same type of organism accounted for our finding so many types.

In spite of all the difficulties that sometimes arise in the diagnosis of a given infection and with all necessary reserve, we believe that there no longer can be

any doubt that, at least in Uruguay, Shigella and Salmonella are responsible for the majority of instances of infantile summer diarrhea and for the majority of deaths, which is the really important point when we have prevention of this disease in mind.

Infections caused by Shigella are more important than those caused by Salmonella in this country. For many years it was believed that bacillary dysentery did not exist in Uruguay, since epidemics in adults have not been reported in the present century, probably because the Shiga type is not prevalent. But since we proved that this is not the case, it has been recognized that this disease is endemic among children. In this respect our investigations confirm those of Cooper and his collaborators in Cincinnati and show that the absolute frequency of dysentery is in inverse proportion to the age of children, while the relative frequency is in direct proportion. We may add that mortality is also in inverse proportion to age.

In our country Salmonella infections are of significance only in relation to children, as food poisoning in adults has been rarely reported and mortality is very low. However, it is necessary to remember that the action of these organisms is not limited to the intestine and that extraintestinal localizations, with or without associated enteritis, are frequent, particularly in the case of infants. As already mentioned, many of our patients who when they were considered exclusively from the point of view of their intestinal syndrome were classified as having plain diarrhea or even as being mere carriers were suffering from angina, otitis or septicemia due to Salmonella. This is important in prophylaxis, as there is no doubt that Salmonella infections are easily transmitted among infants and that urine or feces of a child showing no intestinal disorders can transmit the disease and produce enteritis in children in the same ward of the hospital. As mentioned, we have observed such an outbreak produced by S. cerro in the Casa Maternal.[8] For a number of years we have maintained the opinion, based on observed facts, that in infants the borderline between typhoid-like Salmonella infections and acute enteritis due to these bacilli is not well defined and the pathologic process and epidemiologic characteristics of infantile salmonellosis are very different from those of the infection in adults. Our conception of them is generally known as the "doctrine of Montevideo" [14f] and attempts to explain many facts which are not in accordance with the "doctrine of Kiel," accepted at present by all authors, although not always under this name.

It is evident that in order to solve the problem of prophylaxis of infantile summer diarrhea it is highly desirable to obtain more accurate information concerning its causation and epidemiologic features. All measures taken in this country to improve general hygienic conditions, including pasteurization of milk, which has been compulsory in Montevideo for more than ten years, have had little if any effect on infantile mortality. Infections due to Shigella are exclusively of human origin, and long experience has shown that the elimination of human feces is the first step to be taken in control of these conditions. There is much to do in this direction in our country, and it is significant that infantile diarrhea is more prevalent among the poorer classes, living under poor hygienic conditions in the suburbs of towns, where there is often lack of good disposal of sewage. Education and propaganda will probably lower mortality from infantile diarrhea to a certain extent, as we may expect that at least morbidity of dysentery will decrease. Nevertheless it must be said that we have observed many instances of this disease in well-to-do families living in town, among children constantly supervised by phy-

sicans and even exclusively breast fed. It is probable that healthy adult carriers play a part of unknown importance in the transmission of bacillary dysentery.

As for Salmonella, it is supposed that it is transmitted from animals, domestic or others, to man; if this is the case, we must admit that we do not know how the transmission takes place. It is generally believed that flies are often vectors of intestinal infections, and this seems to be proved beyond doubt in some outbreaks of dysentery. We have started investigations on this line in collaboration with Dr. R. V. Talice, professor of parasitology at the School of Medicine, in which we are trying to determine the relative prevalence of flies in Montevideo in relation to seasons and at the same time to examine them for Shigella and Salmonella. The flies are caught in a special trap devised by us which does not allow them to come in contact with the bait. They are first sorted and classified and then examined in groups of twenty. After thirteen months of daily examinations, in which we employed 7,000 flies, it has been found that Salmonella occurred frequently, especially during the summer months, when about 40 per cent of cultures from our groups of 20 flies gave positive results. In contrast, we have never found Shigella, but we do not think that this failure can be taken as a basis for any conclusions, since our flies were caught in town and the probability of their contact with human feces was slight indeed. Therefore, we consider a campaign against flies advisable for the prevention of diarrhea in children.

Transmission of Salmonella by permanent human carriers is unlikely, as all authors, including ourselves, are of the opinion that such persons are scarce, if they exist at all. We think, though, that not enough attention has been paid to the possibility of transmission by transitory carriers. The latter are rather common, especially among adults and also, as already mentioned, among children. As in the case of dysentery, we have observed enteritis due to Salmonella in children under excellent medical and hygienic care.

SUMMARY

This paper summarizes our investigations on the causation of diarrhea in children carried out in Montevideo from June 1, 1936 to June 1, 1942. We examined 3,592 children who were admitted to hospitals for all causes without regard to intestinal disorders. We looked for Shigella and Salmonella in their stools and in other materials (urine, pus from the middle ear, pharyngeal exudate and blood). Lactose-litmus, S. S. and Leifson's desoxycholate-citrate-agar plates were employed for the isolation of Shigella, and Kristensen, Lester and Jurgens and S. S. agar plates for the isolation of Salmonella. As enrichment mediums we used Liefson's "F" selenite and Kauffmann's "K" tetrathionate. Isolated strains were typed according to their biochemical and serologic behavior and, in the case of Salmonella, according to the Kauffmann and White antigenic schema. The total number of bacteriologic examinations was 9,911.

We isolated 393 strains of Shigella from as many children—327 Flexner, 35 Sonne, 22 Boyd's "88" type, 8 Schmitz and 1 Boyd's "P. 143" type. The Shiga type has never been found in Uruguay. As for Salmonella, we isolated 537 strains from 498 patients. The most prevalent types were S. typhi murium, S. Newport, S. Montevideo, S. anatum, S. paratyphi B. and S. Bredeney. In all we found 29 different types.

In our cases, 668 infections were classified as enteritis (dysenteriform, choleriform or mixed); of them 260 were due to Shigella and 152 to Salmonella and 256 were of unknown origin (38.92 per cent, 22.75 per cent and 38.32 per cent,

respectively). In cases studied during the last two years instances of enteritis due to Shigella and Salmonella amounted together to 57.45 per cent of all instances of enteritis among infants under 1 year of age, to 77.77 per cent in those under 2 years, and to 94.44 per cent in those between 2 and 12 years.

Association of Shigella and Salmonella was often found, as well as association of several types of Salmonella.

Extraintestinal localizations were more frequent in Salmonella than in Shigella infections. Among extraintestinal infections angina, otitis and septicemia were most common.

Salmonella was observed more frequently in patients with mild infections and in intestinal carriers than was Shigella. The carrier state was always transitory.

Institute of Hygiene of the School of Medicine.

Abstracts from Current Literature

Anatomy and Physiology

CHANGES IN LUNG STRUCTURE DURING ASPIRATION OF AMNIOTIC FLUID AND DURING AIR BREATHING AT BIRTH. W. H. WHITEHEAD, W. F. WINDLE and E. BECHURK, Anat. Rec. **83**:255 (June) 1942.

Guinea pigs were used; the trachea was clamped off in some, and others were made to breathe in utero. The authors concluded that intrauterine respiration movements in utero are not strong enough normally to aspirate amniotic fluid. Atelectasis persists till birth. There is some expansion of lung with intrauterine asphyxia. One hour after birth normally the lungs are 40 per cent expanded. The alveoli and alveolar ducts of guinea pigs are lined with cuboidal epithelium at birth. It is suggested that the small amount of fluid and mucoid material usually found in the trachea and lungs is a secretion of this cuboidal epithelium which flows to the surface and prevents the aspiration of vernix, etc., into the alveolar spaces.

SNELLING, Toronto, Canada.

Biochemistry; Bacteriology, and Pathology

A LETHAL AGENT PRODUCED BY THE HEMOLYTIC STREPTOCOCCUS. T. N. HARRIS, J. Bact. **43**:739 (June) 1942.

The author grew beta-hemolytic streptococci of Lancefield group A on meat extract broth, and the streptococci were then removed, after which the sterile filtrate was found to cause immediate death on intravenous injection into rabbits or mice. In smaller doses it was able to produce neuromuscular effects. The author believes that the substance which causes these results is distinct from the soluble hemolysin produced in such cultures. All his tests indicate it to be nonprotein in nature, and he suggests it is probably a small alcohol-soluble molecule, colorless in aqueous solution. This investigation brings up again the problem of lethal substances produced by streptococci. The clarification of this problem and the relations of the substances to each other and to the hemolysin must await further characterization of each one and separation of the substances from each other.

STOESSER, Minneapolis.

GROWTH REQUIREMENTS OF THE MENINGOCOCCUS. IVAN D. FRANTZ JR., J. Bact. **43**:757 (June) 1942.

The author employed type I meningococcus organisms in his study of the growth requirements of the organism. After numerous experiments he found that the following composition in gram per liter yielded the best medium:

d-Glutamic acid	1.3	NaCl	6.0
l-Cystine	0.012	NH_4Cl	1.25
$NAH_2PO_4H_2O$	2.5	$MgSo_4.7H_2O$	0.6
KCl	0.09	Glucose	5.0

This preparation appears to overcome the difficulty in cultivating the meningococcus. Primary isolation of the organism was not attempted. However, fourteen of fifteen strains of meningococci in early generations could easily be cultivated on the liquid medium. For further details reference to the original paper is recommended.

STOESSER, Minneapolis.

INFLUENZA VIRUS B: I. OBSERVATION ON GROWTH IN CHICK EMBRYOS AND ON THE OCCURRENCE OF ANTIBODIES IN AUSTRALIAN SERUM. F. M. BURNET, M. J. Australia **1**:671 (June 20) 1942.

Burnet reports that influenza virus B (Francis strain) can be grown in chick embryos inoculated either by amniotic or by suballantoic methods. The lesions produced are entirely similar to those of influenza virus A. Tests with human serum taken in Australia indicate that infections with influenza virus B have occurred in recent years, in 1 subject the attack of infection dating back to November 1938. Hirst's method of titrating virus and antiserum is applicable to influenza virus B, and two applications of the method are described.

GONCE, Madison, Wis.

INFLUENZA VIRUS B: II. IMMUNIZATION OF HUMAN VOLUNTEERS WITH LIVING ATTENUATED VIRUS. F. M. BURNET, M. J. Australia **1**:673 (June 20) 1942.

Living influenza virus B adapted to chick embryo passage was administered intranasally to volunteer subjects. The material for immunization was prepared by the inoculation of thirty-ninth passage seed virus into twelve day eggs by the suballantoic method. Subjects with initially low level of antibody as judged by Hirst's method responded with a significant increase in antibody level. Only trivial symptoms or none at all were observed. It is possible that this technic may provide a useful method of immunization against influenza virus B.

GONCE, Madison, Wis.

Metabolism; Infant Feeding; Milk and Other Foods

THE PRESENCE OF INGESTED COTTONSEED PROTEIN IN WOMAN'S MILK. MATTHEW BRUNNER and BESSIE BARON, J. Allergy **13**:358 (May) 1942.

The presence of cottonseed protein in woman's milk after ingestion of a cottonseed meal (5 to 20 Gm. of dehulled cottonseed ground to a fine powder and mixed with 30 cc. of water) was demonstrated by a passive transfer technic. Specimens obtained during the first two hours following the ingestion from 6 of the subjects contained no antigen. Of 18 specimens obtained two to twenty-four hours after ingestion of the protein, the antigen was present in 39 per cent and doubtfully present in 22 per cent.

The experiment duplicates the results obtained by Donnally, which showed that egg white ingested by a nursing mother can be demonstrated in her milk by passive transfer technic.

HOYER, Cincinnati.

THE EFFECTS OF THE SUBSTITUTION OF BICARBONATE FOR CHLORIDE IN THE DIET OF RATS ON GROWTH, ENERGY AND PROTEIN METABOLISM. LEROY VORIS and E. J. THACKER, J. Nutrition **23**:365 (April) 1942.

The nutritional effects of a deficiency of dietary chlorides in rats' diets were, according to Voris and Thacker, comparable to those of a general mineral deficiency. These rats showed anorexia, increased consumption of water and a diminished gain of nitrogen in the body and of energy.

FREDEEN, Kansas City, Mo.

THE INFLUENCE OF DIETARY FAT ON LACTATION PERFORMANCE IN RATS. L. A. MAYNARD and EDITH RASMUSSEN, J. Nutrition **23**:385 (April) 1942.

Maynard and Rasmussen found an increased lactation performance in rats fed a high fat diet, as indicated by the superiority in growth and dry matter content of their offspring.

FREDEEN, Kansas City, Mo.

A FURTHER INVESTIGATION OF BREAST FEEDING. MARGARET ROBINSON, Arch. Dis. Childhood **17**:23 (March) 1942.

A study of 1,000 mothers was undertaken to find the cause of variation in rate of breast feeding. The mothers were divided into 4 groups as follows: (1) mothers all of whose children were fully breast fed; (2) mothers all of whose children were weaned early; (3) mothers whose older children were weaned early and many of whose younger ones were fully breast fed, and (4) mothers whose older children were fully breast fed and many of whose younger ones were weaned early.

The swing in the breast feeding rate depends on the variations in the percentage of these types. Breast feeding is not affected by the following: the seasons of the year, the parity of the mother, the age of the mother, the size of the breasts, the antepartum presence of secretion in the breasts, the return of menstruation, rheumatic endocarditis, simple enlargement of the thyroid gland, preeclampsia and antepartum symptoms relieved by calcium. Breast feeding is affected by the following factors: size and character of the nipple, masculinity, obesity, morning sickness, pyelitis, severe varicose veins, breast abscesses and cracked nipples. Fifty-two per cent of early weaning occurs in all types before the end of the first month.

KELLY, Milwaukee.

Vitamins; Avitaminoses

SCURVY IN MONTREAL. D. G. CAMERON and E. S. MILLS, Canad. M. A. J. **46**:548 (June) 1942.

There may be an absence of clinical signs of scurvy for several weeks after the plasma ascorbic acid level has become zero. A patient is described in whom the plasma ascorbic acid

level was zero and the hemorrhagic signs and articular pains of scurvy were present but in whom the gingival lesions were absent. The hemorrhagic symptoms cleared up with the administration of vitamin P (hesperidine) but the articular pains did not clear up until vitamin C was given.

It is important to study both the urinary excretion and the plasma level of ascorbic acid in order to get a true idea of the vitamin C deficiency.

MOORE, Omaha.

THE EFFECT OF THE LEVEL OF FAT IN THE DIET UPON UTILIZATION OF VITAMIN A. KATHLEEN DIETRICH MUELDER and EUNICE KELLY, J. Nutrition **23**:335 (April) 1942.

Muelder and Kelly found that the amount of intake of vitamin A was a more significant factor than the level of dietary fat in the production of gain in weight, growth in length and reduction in number of "abscesses" in rats.

FREDEEN, Kansas City, Mo.

VITAMIN A REQUIREMENTS IN THE RAT: THE RELATION OF VITAMIN A INTAKE TO GROWTH AND TO CONCENTRATION OF VITAMIN A IN THE BLOOD PLASMA, LIVER AND RETINA. J. M. LEWIS, O. BODANSKY, K. G. FALK and G. MCGUIRE, J. Nutrition **23**:351 (April) 1942.

Lewis and co-workers noted that the minimum and optimum vitamin A requirements are of the same order for rats and for infants. The minimum requirement for rats was 2 U. S. P. units daily, or 20 units per kilogram. Optimal growth occurred with an intake of 25 units daily; optimal blood concentrations, with an intake of 50 units daily, and good reserves in the liver, with an intake of 100 units daily. These investigators concluded that concentration of the vitamin in the blood is a more sensitive indication of vitamin A deficiency than the dark adaptation test.

FREDEEN, Kansas City, Mo.

ASCORBIC ACID EXCRETION AT KNOWN LEVELS OF INTAKE AS RELATED TO CAPILLARY RESISTANCE, DIETARY ESTIMATES AND HUMAN REQUIREMENTS. TATIANA LEVCOWICH and E. L. BATCHELDER, J. Nutrition **23**:399 (April) 1942.

Levcowich and Batchelder in a survey study on 45 young women concluded that capillary resistance was not significantly affected by variation in known intake of crystalline ascorbic acid, but suggested rather that there was a lack of vitamin P or some other factor affecting capillary fragility. The urinary excretion of the acid during a period when the diet was deficient in vitamin C dropped sharply during the first twenty-four hours and reached a constant resting level within forty-eight hours. Their data indicated that the minimal requirement of ascorbic acid for a moderately active young woman is 50 mg. and a dietary standard is 75 mg. daily.

FREDEEN, Kansas City, Mo.

THE DISTRIBUTION OF NICOTINIC ACID IN FOODS. L. J. TEPLY, F. M. STRONG and C. A. ELVEHJEM, J. Nutrition **23**:417 (April) 1942.

Tepley, Strong and Elvehjem in their study using the microbiologic assay of foods for nicotinic acid reported that meats in general, particularly the organs, yeast and peanut butter are excellent sources. The nicotinic acid content of a variety of foods was reported.

FREDEEN, Kansas City, Mo.

THE FATE OF EXCESS VITAMIN A STORES DURING DEPLETION VALUE OF THE HISTOLOGIC DEMONSTRATION OF VITAMIN A. HANS POPPER and SADIE BRENNER, J. Nutrition **23**:431 (May) 1942.

Popper and Brenner in their study made chemical and histologic examinations of the liver with various gradations of the vitamin A content, thereby evaluating the histologic method for demonstration of vitamin A. Parallelism between the vitamin A fluorescence of the liver and that of the retina or the vitamin A level of the blood did not exist. The Kupffer cells stored the excess vitamin A during hypervitaminosis and apparently destroyed it, which explains the uneconomical utilization of vitamin A under conditions of excess supply. In depletion, the Kupffer cells distributed the remnants of vitamin A.

FREDEEN, Kansas City, Mo.

THE RELATION OF LIVER STORES TO THE OCCURRENCE OF EARLY SIGNS OF VITAMIN A DEFICIENCY IN THE WHITE RAT. SADIE BRENNER, MARGARET C. HESSLER BROOKES and LYDIA J. ROBERTS, J. Nutrition **23**:459 (May) 1942.

Brenner and her co-workers from their study concluded that for rats the use of the vitamin A content of the blood or retina or histologic changes in the skin as early detectors

of vitamin A deficiency is not warranted if the deficiency means lack of liver stores. In the absence of liver stores all three of these measurements were resistant to change. The females stored and retained more vitamin A in the liver than the males, while the males had higher blood levels.

FREDEEN, Kansas City, Mo.

THE DAILY INTAKE OF ASCORBIC ACID REQUIRED TO MAINTAIN ADEQUATE AND OPTIMAL LEVELS OF THIS VITAMIN IN BLOOD PLASMA. MARGARET L. FINCKE and VIRGINIA L. LANDQUIST, J. Nutrition **23**:483 (May) 1942.

The daily intake of ascorbic acid necessary to maintain saturation in young adults was found by Fincke and Landquist to be 111 to 131 mg., or 1.7 to 2 mg. per kilogram of body weight.

FREDEEN, Kansas City, Mo.

STUDIES ON THE VITAMIN B COMPLEX IN THE NUTRITION OF THE DOG. A. E. SCHAEFER, J. M. MCKIBBIN and C. A. ELVEHJEM, J. Nutrition **23**:491 (May) 1942.

Schaefer, McKibbin and Elvehjem found that in the diet of the dog liver extract must be given in addition to a highly purified vitamin B complex–free ration supplemented with thiamine, riboflavin, nicotinic acid, pyridoxine, pantothenic acid and choline to produce optimal growth. The identity of the substance or substances in liver extract responsible for the improvement could not be established from this study.

FREDEEN, Kansas City, Mo.

RELATIONSHIP BETWEEN PANTOTHENIC ACID REQUIREMENT AND AGE IN THE RAT. KLAUS UNNA and GRACE V. RICHARDS, J. Nutrition **23**:545 (June) 1942.

Unna and Richards studied the pantothenic acid requirement at various stages of life of albino and piebald rats maintained on a basal diet free of pantothenic acid. They found that the maintenance dose for optimal growth and prevention of deficiency lesions decreased from 100 micrograms per day at 3 weeks to 25 micrograms per day at 10 weeks of age.

FREDEEN, Kansas City, Mo.

THIAMINE, RIBOFLAVIN, PYRIDOXINE AND PANTOTHENATE DEFICIENCIES AS AFFECTING THE APPETITE AND GROWTH OF THE ALBINO RAT. LEROY VORIS, ALEX BLACK, R. W. SWIFT and C. E. FRENCH, J. Nutrition **23**:555 (June) 1942.

Voris and his associates used paired feeding methods to distinguish the effects on appetite and growth of rats with moderate deficiencies of thiamine, riboflavin, pyridoxine and calcium pantothenate. All four vitamins had a definite positive effect on appetite. Riboflavin, pyridoxine and pantothenate had specific growth-promoting effects unrelated to appetite. Thiamine improved the growth of female rats, but no effect was noted in males by addition of liver extract to the so-called complete synthetic diet; neither appetite nor growth was improved.

FREDEEN, Kansas City, Mo.

THE EFFECT OF A HIGH VITAMIN A INTAKE ON THE BLOOD AND MILK CAROTENE OF HOLSTEIN AND GUERNSEY COWS. HARRY J. DEUEL JR., LOIS F. HALLMAN, CORNELIA JOHNSTON and FRED MATTSON, J. Nutrition **23**:567 (June) 1942.

Deuel and associates noted in their studies that the amount of carotene in the milk decreased after administration of vitamin A and that the carotene in the blood decreased concomitantly. A proportionality exists between the levels of carotene in the blood and in the milk; the slopes of the curves for the Guernsey and the Holstein cows were similar, but for the latter breed the values were at a much lower level.

FREDEEN, Kansas City, Mo.

VITAMIN CONTENT OF HONEYS. M. H. HAYDAK, L. S. PALMER, M. C. TANQUARY and A. E. VIVINO, J. Nutrition **23**:581 (June) 1942.

Haydak and co-workers showed by microchemical and microbiologic determinations that the 67 samples of honey studied contained thiamine, riboflavin, ascorbic acid, pyridoxine, pantothenic acid and nicotinic acid. The amount was extremely variable, depending probably on the source of the honey and the number of pollen grains present in the product. The most pronounced variations were in nicotinic and ascorbic acid content. Tables are presented showing a statistical study of the various honeys.

FREDEEN, Kansas City, Mo.

STUDIES OF THE AVERAGE AMERICAN DIET: I. THIAMINE CONTENT. ROBERT L. LANE, ELIZABETH JOHNSON and ROBERT R. WILLIAMS, J. Nutrition **23**:613 (June) 1942.

Lane, Johnson and Williams found that prior to the advent of enriched bread, approximately 75 per cent of the American population consumed 0.8 mg. of thiamine per 2,500 calories. If the consumption of enriched bread becomes universal, the average intake will be increased about 64 per cent, to about 1.3 mg. per 2,500 calories. Lean pork, bread and milk are the principal sources of thiamine in the prevailing diets. Tables are given for the thiamine content of foods.

FREDEEN, Kansas City, Mo.

VITAMIN E, COD LIVER OIL AND MUSCULAR DYSTROPHY. H. A. MATTILL and CALVIN GOLUMBIC, J. Nutrition **23**:625 (June) 1942.

Mattill and Golumbic presented evidence to show that no distinction need be made between muscular dystrophy induced by cod liver oil and that produced by lack of vitamin E in the diet. The vitamin B complex factors apparently are not concerned with nutritional muscular dystrophy.

FREDEEN, Kansas City, Mo.

THE VITAMIN E CONTENT OF CERTAIN VARIETIES OF WHEAT, CORN, GRASSES AND LEGUMES AS DETERMINED BY RAT ASSAY. C. A. CABELL and N. R. ELLIS, J. Nutrition **23**:633 (June) 1942.

Cabell and Ellis used a modified biologic assay method for vitamin E in which alpha tocopherol is made the basis of estimation. The vitamin E content of five varieties of wheat was found to be 2.3 to 5.4 mg. of equivalent alpha tocopherol per hundred grams of grain; of six varieties of corn, 1.5 to 3.6 mg., and of five species of dried and green grasses and legumes, 7.1 to 28.1 mg.

FREDEEN, Kansas City, Mo.

VITAMIN B_1 AND ENDURANCE. PETER V. KARPOVICH and NATHAN MILLMAN, New England J. Med. **226**:881 (May 28) 1942.

Recent reports have indicated that the administration of vitamin B_1 may increase muscular endurance in subjects on a diet deficient in that vitamin. This effect is explained on the basis of the role of vitamin B_1 as an oxidative catalyst employed in the chemical process involved in muscular contraction.

Arm-Holding Test.—Sixty-nine subjects, all of college age, were tested for the time they were able to hold their arms horizontally. Forty-one of the 50 men whose arm-holding times were less than thirty minutes were given either 5 mg. of thiamine hydrochloride a day or a placebo (5 mg. of lactose).

A week later, the second test was given, the range varying from five to seventy-seven minutes in the group who did not receive the vitamin and from seven to seventy-nine minutes in the men who did.

The Breath-Holding Test.—The authors used a group of 20 men for this experiment. There were given two breath-holding tests in succession, and then half the subjects were put on a diet containing 5 mg. of thiamine chloride a day for a week, and half on one containing 5 mg. of lactose a day. No effect of vitamin B_1 on breath-holding ability was observed.

These tests may be greatly affected by psychologic factors and are therefore not reliable indications of the degree of muscular endurance.

GENGENBACH, Denver.

COMPARISON OF VITAMIN A OF LIVER BIOPSY SPECIMENS WITH PLASMA VITAMIN A IN MAN. KARL A. MEYER, HANS POPPER, FREDERICK STEIGMANN, WILLIAM H. WALTERS and SOL ZEVIN, Proc. Soc. Exper. Biol. & Med. **49**:589 (April) 1942.

Determinations of the vitamin A content of biopsy specimens of the liver and specimens of blood taken before, during and after operation from 34 patients with various diseases of the upper part of the abdomen requiring operation revealed no relationship to exist in the amount of this vitamin in the blood and in the liver. Patients with high blood levels had at least average stores in the liver.

HANSEN, Minneapolis.

VITAMIN C IN FRUIT PREPARATIONS. J. M. ALSTON, Brit. M. J. **1**:559 (May 2) 1942.

Sixteen fruit preparations were tested for vitamin C content, and the amounts of vitamin C found are listed in this article. Also one preparation was tested at the time the tin was opened and after it had been exposed to air for various periods. The figures for the vitamin C content of this preparation are also listed. The article is short and does not lend itself to abstracting. However, the article is summarized in one sentence as follows: "It would appear,

therefore, that the vitamin is likely to remain comparatively stable in black currant purée and rose-hip syrup if these are kept in tins or bottles which are air-tight and contain the minimum residual air."

BIRDSONG, University, Va.

INFANTILE BERI-BERI. D. V. S. REDDI, Indian J. Pediat. **9**:57 (April) 1942.

Reports from other observers confirm Reddi's earlier contention that the breast milk of women deficient in vitamin B_1 contains a toxic substance that may produce acute and even rapidly fatal illness in the infant. Toxic milk is identified by the peroxidase reaction, and the toxic substance is similar to methylglyoxal (pyruvaldehyde). The peroxidase reaction reverses after vitamin B_1 is administered for a few days to the mother. TENNEY, Madison, Wis.

VITAMIN-C LEVELS OF SCHOOL CHILDREN AND STUDENTS IN WAR-TIME. LESLIE J. HARRIS, Lancet **1**:642 (May 30) 1942.

Children at an elementary school in a poor district and at a well conducted residential institution were examined for their levels of vitamin C. Both groups had considerably lower levels than the corresponding groups examined before the war. As in previous surveys, those from children at the institution were found to be higher. Middle class university students and scientific workers seemed on the whole to have been affected less than the poorer children in their reserves of vitamin C. "Few foods rich in vitamin C are available at present during the winter. Indeed unless good helpings of potatoes and greenstuffs (sprouts, cabbage, & c.) are taken it is difficult to see how the reputed requirement can be attained. Roughly 11 oz. of boiled potatoes each day or 15 oz. of cabbage weekly would be needed to provide only 15 mg. of the daily 30 mg. (League of Nations Requirement)." LANGMANN, New York.

PELLAGRIN'S PROGRESS. A. R. R. MEARS, South African M. J. **16**:147 (April 11) 1942.

The author emphasizes his observation that among the local natives of Cape Province, stomatitis and in particular ulceration of the lower lip, is often the first sign of a pellagric condition.

GONCE, Madison, Wis.

BLOOD PHOSPHATASE IN RICKETS IN CUBA. ANTONIO SELLEK AZZI and ELADIO DE CASTRO, Arch. de med. inf. **11**:52 (April-June) 1942.

The blood phosphatase level is rarely increased in persons who live in Cuba, usually not above 20 Bodansky units. This is no doubt due to the increased amount of ultraviolet rays, which make rickets a sporadic and mild disease in Cuba.

SANFORD, Chicago.

Hygiene; Growth and Nutrition; Public Health

THE VARIABILITY OF WEIGHT AND HEIGHT INCREMENTS FROM BIRTH TO SIX YEARS. MEINHARD ROBINOW, Child Development **13**:159 (June) 1942.

"Increments of growth are more valuable than attainment of growth as indicators of children's progress. Mean increments of height and weight can be obtained from the usual height and weight tables. But the variability of increments must be calculated from raw data.

"Norms are presented for increments of height and weight and their standard deviations for successive age intervals from birth to six years.

"The variability of these increments presents several problems of theoretical and practical interest."

[AUTHOR'S SUMMARY]

INDEXES OF THE MASS AND BODY PROPORTIONS OF MINORS. ANTONIO CUNHA, Bol. serv. Soc. d. Menores **2**:45 (March) 1942.

From tables of weights, sizes and chest measurements from the Test Institute the author concludes that the minors examined present a "brevilineal" morphologic type and that boys are undersized and girls oversized relative to the weight of the body. He also believes that the food factor which has influence in the somatic evolution of the minors, especially boys, should be further investigated.

SANFORD, Chicago.

Prematurity and Congenital Deformities

PLATYBASIA, KLIPPEL-FEIL SYNDROME AND SPRENGEL'S DEFORMITY. WILLIAM FURST and HERMAN W. OSTRUM, Am. J. Roentgenol. **47**:588 (April) 1942.

The simultaneous occurrence of these three rare developmental anomalies in the same patient was reported. The patient, a Negro 29 years of age, was admitted to the hospital

after a generalized convulsion. For the preceding six years he had drunk excessively and had had a right-sided morning headache relieved by fainting or by sleep. Generalized epileptiform convulsions occurred first about three years previous to his admission and had been recurring about every two weeks since.

A physical examination showed pronounced upward displacement of the left shoulder, short neck and flaring trapezii, with moderate limitation of movement of the neck in all directions and with atrophy of the muscles of the left shoulder girdle. Neurologic findings were: a left central facial weakness, loss of the associated movements of the left arm and increased left but absent right biceps reflex. The patient admitted being addicted to mariahuana. He was treated in the psychopathic ward without medication. In a follow-up study six months later he had been free of convulsions since abstaining from alcohol and mariahuana.

Roentgen examination showed a flattened, stenosed foramen magnum. The first cervical vertebra was higher than normal and extended into the foramen magnum. There was fusion of the second and third cervical vertebrae with congenital spina bifida and hemivertebrae in the lower and upper thoracic regions. The left scapula was small and elevated.

The authors consider a common congenital etiologic relationship for platybasia, the Klippel-Feil syndrome and Sprengel's deformity. SQUIRE, Chicago.

CONGENITAL MALFORMATIONS INDUCED IN RATS BY MATERNAL NUTRITIONAL DEFICIENCY. JOSEF WARKANY and ROSE C. NELSON, J. Nutrition **23**:321 (April) 1942.

When the maternal diet of a rat contained liver or its alcoholic extract, the offspring were protected from congenital malformations. Warkany and Nelson are conducting further investigations in an attempt to determine the factor responsible. FREDEEN, Kansas City, Mo.

THE SCALENUS ANTICUS FACTOR IN CONGENITAL TORTICOLLIS. SIDNEY M. COPELAND, Surgery **11**:624, 1942.

Copeland reports 3 cases in which resistance to overcorrection of torticollis was noted at operation after the appropriate sternocleidomastoid muscle had been cut. In each case hypertrophy of the scalenus anticus muscle was the obstructing factor, and severance of this additional muscle was followed by an excellent result in all 3 cases. Injury at birth was thought to have been the significant etiologic factor in these cases. The scalenus muscle may have become short secondary to injury and fibrosis of the overlying sternocleidomastoid, or it may have suffered primary injury itself. Exploration of the scalenus anticus muscle is recommended during all operations for torticollis.

DRAYER, Philadelphia. [ARCH. NEUROL & PSYCHIAT.]

FETAL CIRCULATION AND ITS CHANGES AT THE TIME OF BIRTH. W. BONIN, Union méd. du Canada **71**:457 (May) 1942.

The theory of fetal circulation as originally described by Sabatier in 1774 has been altered very little since its conception. Numerous studies have served but to change its form in minor details. Bonin, working from the measurements of the various orifices of the fetal heart, advances an entirely new explanation. There are three weak points in the Sabatier theory: (1) It does not explain how the lower part of the body receives adequate oxygenation; (2) it assumes that the pulmonary circulation is infinitesimal, and (3) it explains the closure of the foramen ovale by postulating an increase in pressure in the left auricle.

Bonin states that blood from the inferior vena cava passes in nearly equal amounts to both sides of the heart. Blood from the superior vena cava goes entirely into the right ventricle while that from the pulmonary veins goes entirely into the left ventricle. Thus the ventricles contain equal amounts of oxygenated and venous blood and distribute the oxygenated blood equally through the upper and lower portions of the fetus.

Apneic lungs are full of blood; their vessels are fully developed. Patten has shown that there is no difference in resistance to injecting atelectatic and expanded lungs. Moreover, the research of Abel and Windle has shown that there is no increase in pulmonary circulation after birth.

The closure of the foramen ovale is most probably due to the lowering of pressure within the right auricle as the umbilical vein ceases to flood it. Researches of Hamilton and co-workers and of Patten confirm this view.

The cause of the closure of the ductus arteriosus is still unknown. DAFFINEE, Boston.

PREMATURITY AND THE HIGH SCOTTISH INFANT DEATH RATE. CHARLES MCNEIL, Glasgow M. J. **19**:87 (April) 1942.

The author points out that premature infants provide a large proportion of the deaths that make the Scottish infant death rate so high. He makes a plea for better care of premature babies during the first month. He shows that the organs such as the lungs and stomach are immature. He advocates closer cooperation between the pediatrician and the obstetrician. The obstetrician, by improving the health of mothers, can often prolong the gestation of the baby.

SNELLING, Toronto, Canada.

CONGENITAL EVENTRATION OF THE DIAPHRAGM. S. RAO, J. Indian M. A. **11**:243 (May) 1942.

Congenital eventration of the diaphragm was discovered in a young adult who complained of low grade fever, slight cough and a gradual loss of weight over a period of three months. Eventrations have been classified into three types: (1) congenital, occurring in the left side almost exclusively; (2) secondary to paralysis of the nerve, occurring equally on the two sides, and (3) secondary to megacolon. The affected dome of the diaphragm is composed of a thin fibrous sheet rising to the third or fourth interspace. The congenital form must be differentiated from (1) temporary elevation due to gaseous distention of the stomach, (2) hernia of the diaphragm and (3) injury to the phrenic nerve due to avulsion, trauma, cancer or mediastinal glands or tumors, tuberculosis, Hodgkin's disease, etc.

GONCE, Madison, Wis.

TREATMENT OF HARELIP AND CLEFT PALATE. DAGMAR A. CHAVES, Rev. méd. munic. **3**:259 (March) 1942.

The author describes the clinical characteristics of this anomaly. He uses Veau's operation to repair the palate, usually doing this between 2 and 3 years of age. The operation for harelip depends on each individual instance. Photographs are shown of the results, which are uniformly good.

SANFORD, Chicago.

ALTERATIONS OF MUSCULAR AUTOMATISM DURING EMBRYONAL DEVELOPMENT, INVESTIGATED BY IN VITRO CULTURES. J. SZEPSENWOL, Rev. Soc. argent. de biol. **18**:71 (May) 1942.

Somatic muscles of chick embryos the incubation time of which varied from ten days up to the time of hatching and of chicks aged from 1 to 10 days were cultivated in a hanging drop in order to study the changes in contractibility which may occur during development. It has been established that the automatic activity of the somatic muscle increases until the fourteenth day of incubation and then begins to decrease, disappearing completely at hatching. While explanted somatic muscle from a 12 to 14 day embryo starts to contract after twenty-four hours of cultivation, the same sort of tissue of a 15 to 17 day embryo does not manifest spontaneous contractions until the fifth day of growth in vitro.

MCCUNE, New York.

INFLUENCE OF BARIUM CHLORIDE AND OF POTASSIUM CHLORIDE ON CULTURES OF THE MYOCARDIUM AND OF SOMATIC MUSCLES OF THE CHICK EMBRYO. E. SACERDOTE DE LUSTIG. Rev. Soc. argent. de biol. **18**:146 (May) 1942.

The myocardium of twenty-four to forty-eight hour old chick embryos was cultivated in vitro. With low concentrations of barium chloride in the medium, contractions appear later than normally, and their rhythm remains slow. The addition of a drop of Ringer's solution which contains from 2.5 to 5 per cent of barium chloride two days after explantation in a normal medium produces immediately a slow rhythm and half an hour later a complete paralysis. After two to three days contractions appear again. The somatic muscle of 8 to 13 day old embryos treated with 0.2 per cent barium chloride two to seven days after explantation is paralyzed immediately and definitively. In all these cases there is a complete agenesis or destruction of the myofibrillae.

Potassium chloride in various concentrations added at the beginning or during the culture of myocardium (1 to 2 day old chick embryos) produces paralysis but does not prevent the differentiation of the myofibrillae. Its effect on the somatic muscle appears to be less intense than on the myocardium.

These results are interpreted as supporting the hypothesis that both the myofibrillae and the sarcoplasm are contractile.

MCCUNE, New York.

Newborn

ACUTE LARYNGOTRACHEOBRONCHITIS IN A NEWBORN INFANT: REPORT OF A CASE WITH RECOVERY FOLLOWING TRACHEOTOMY. MERRILL W. MICHELS, Arch. Otolaryng. **35**:423 (March) 1942.

The recovery of a 5 week old infant with acute laryngotracheobronchitis who required bronchoscopy, tracheotomy, repeated tubal aspirations and chemotherapy is reported. Erosion of the soft palate, caused by a nipple shield, with subsequent descending streptococcic infection is considered as a possible contributing etiologic factor.

GREENWOOD, Chicago.

TACHYCARDIA IN THE NEWBORN. HERMAN TARNOWER and BERTON LATTIN, New York State J. Med. **42**:805 (April 15) 1942.

Tarnower and Lattin report 2 cases of tachycardia in newborn infants. In the first the fetal heart was grossly irregular in rhythm and rate, varying between 140 and 210 beats per minute. After delivery the child seemed normal in every respect except that the irregularity persisted and the rate varied between 140 and 225. Later digitalis was given intramuscularly, and the heart rate was reduced to 136. An electrocardiogram on the first day showed auricular flutter and varying degrees of block. At present the child is normal in all respects, and cardiac murmurs are not heard.

In the second case auriculoventricular nodal tachycardia was found in a 10 day old child. The heart rate was 256, and the child looked critically ill. Digitalis was administered intramuscularly at 9:30 p. m. At 2 a. m. the rate was 125 and regular in force and rhythm. There have been no recurrences of the trouble, and an electrocardiogram taken at the age of 5 months was normal. Tarnower and Lattin feel that digitalis may be satisfactorily employed in paroxysmal tachycardia of the newborn with a fair margin of safety.

AIKMAN, Rochester, N. Y.

THE MANAGEMENT OF FOOT DEFORMITIES IN THE NEWBORN. FREDERICK R. THOMPSON, New York State J. Med. **42**:958 (May 15) 1942.

The foot of the newborn infant is so flexible that it can be moved into an extreme valgus position or into such a varus position that it looks like a severe clubfoot. Deformities are essentially due to contracture. The diagnosis can be made when the foot cannot be passively corrected, but it is better to have roentgen studies for both diagnosis and treatment. While heredity plays some part, excessive uterine pressure can force the feet into positions that produce deformity.

In treatment a slow stretching of the contracted tissues is necessary, and they must be held in corrected positions for long periods of time, usually three months. The secret of success is to start the treatment very early, within the first day or two of life. Then the foot has a chance to grow in the correct position. Delayed treatment is more difficult and less successful. The treatment of accessory toes depends on the roentgenogram of the foot. It is not a good practice to tie a string around the extra toe unless the toe is a mere nubbin attached to the foot by a pedicle of skin.

AIKMAN, Rochester, N. Y.

APNEA NEONATORUM. P. P. VOLPITTO and R. TORPIN, South. M. J. **35**:559 (June) 1942.

The authors believe that apnea neonatorum is responsible for an appalling yearly infant mortality. Effort to reduce the large number of deaths should be directed first toward the elimination of the possible causes, namely, the injudicious use of agents for producing amnesia, analgesia and anesthesia and the unwise and promiscuous employment of operative intervention when not absolutely indicated.

Apnea when present in a newborn infant can be combated easily if immediate action is taken and simple but adequate means of oxygenating the infant's lungs are employed.

SCHLUTZ, Chicago.

A STUDY OF 200 DEATHS ASSOCIATED WITH CESAREAN SECTION 1934 TO 1940 INCLUSIVE. W. C. KEETTEL, Wisconsin M. J. **41**:395 (May) 1942.

By 200 cesarean sections 205 babies were born. There were 33 stillbirths, and 25 more of the babies died before leaving the hospital.

In cases (31) of placenta praevia and abruptio placentae the fetal mortality rate was 61.3 per cent. In 59 cases of eclampsia and other toxemias it was 28.8 per cent; in 42 cases of prolonged labor, uterine inertia and malpresentation, 16.7 per cent, and in 37 cases of disproportion and contracted pelvis, 2.7 per cent.

It will be noted that this is a statistical report and that the deaths occurred entirely among infants whose mothers died.

JANNEY, Wauwatosa, Wis.

A FOURTH TYPE OF ERYTHROBLASTOSIS FOETALIS SHOWING HEPATIC CIRRHOSIS IN THE MACERATED FOETUS. J. L. HENDERSON, Arch. Dis. Childhood **17**:49 (March) 1942.

Three cases of erythroblastosis with hepatic cirrhosis in a macerated fetus are described and autopsy observations are given in detail. The pronounced degree of hepatic cirrhosis proves that erythroblastosis may run a long intrauterine course and is a severe manifestation of the disease.

KELLY, Milwaukee.

GASTRIC ACIDITY IN THE NEW BORN. R. DUTT-CHAUDHURI and K. C. CHAUDHURI, Indian J. Pediat. **9**:77 (April) 1942.

Gastric analyses were made on 108 newborn infants ranging in age from a few minutes to 27 hours. Achlorhydria was found several times. There seems to be a definite relation between body weight and gastric acidity, as the higher figures were found in the larger infants. Complications such as toxemia of pregnancy and operative delivery seemed to have no relation to gastric acidity.

TENNEY, Madison, Wis.

Acute Contagious Diseases

MYOCARDITIS IN POLIOMYELITIS. OTTO SAPHIR and SIMON A. WILE, Am. J. M. Sc. **203**:781 (June) 1942.

The authors report on 7 patients with poliomyelitis, 6 of whom showed evidence at autopsy of varying degrees of myocarditis. Clinically, myocarditis could have been suspected in 3 patients because of a sudden "turn for the worse" without apparent cause, coincident with a rise in pulse rate and cyanosis. The myocarditis was characterized histologically by foci of perivascular infiltrations of lymphocytes and neutrophils. Foci of lymphocytes were also seen just beneath the endocardium. Though the number of inflammatory cells was never large in any one area, they were present in many blocks cut from different parts of the myocardium. The relation of the myocarditis to the bronchopneumonia which was present in 4 of the 7 patients is discussed. The high incidence of myocarditis in this series warrants the consideration of supportive measures. The sudden death of 3 of these patients may be attributed to the myocarditis.

HENSKE, Omaha.

MENINGOCOCCAL SEPTICAEMIA. W. S. C. COPEMAN, Brit. M. J. **1**:760 (June 20) 1942.

Fifteen cases of meningococcic septicemia are reported. These cases do not represent an epidemic, but are sporadic cases occurring at various points and found in the wards of a military hospital from September 1941 to March 1942. All but 1 of the patients had been sent in with another diagnosis, but cultures of the blood of 4 of the 15 were positive for meningococci, although it was occasionally necessary to get more than one culture to recover the organism. The clinical diagnosis of this condition is not particularly difficult if the possibility of the disease is kept in mind. Onset is usually sudden with fever, occasional sweating and a rigor. Pains are frequently found in the muscles and joints, sometimes with effusion. Patients generally are not particularly sick, and one of the characteristic symptoms is a rash which forms pinkish papules, macules and sometimes nodules. These areas blanch on pressure, but occasionally a small hemorrhagic center can be seen. These areas are frequently tender. Enlargement of the spleen is not common. Fever is usually of the septic type, rising to 104 or 105 F. A curious feature of the condition is the absence of wasting, debility or even a feeling of real illness throughout its course.

The treatment consists of the use of sulfapyridine, administration of the drug being continued for about a week after pyrexia has ceased. The patients convalesce rapidly and normally. A chart accompanies this article in which the pertinent data are given on each case. In the comment the author states it is believed that meningococcic septicemia is a comparatively common disease, although it is frequently misdiagnosed, generally as rheumatic fever or influenza.

BIRDSONG, University, Va.

ANTIGENIC PROPERTIES OF H. PERTUSSIS IN RELATION TO ACTIVE IMMUNIZATION. D. G. EVANS, Lancet **1**:529 (May 2) 1942.

"Experiments have shown that a toxic extract of Haemophilus pertussis obtained by disruption of bacilli by physical methods when detoxified with formaldehyde is capable of producing antitoxin and antibacterial antibody on injection into rabbits. A suspension of

whole bacilli treated with formaldehyde did not act in the same way, but only gave antibacterial antibody, as did heated bacilli and heated extract.

"It is suggested that any investigation into new types of vaccine for prophylactic immunization against whooping-cough should take into consideration the significance of the toxin in infection and the value of the toxoid as an immunizing agent. By using a vaccine capable of stimulating the production of antitoxin in addition to antibacterial antibody a more complete protection may be established than that which has hitherto been obtained."

LANGMANN, New York. [AUTHOR'S SUMMARY]

CHRONIC NASAL DIPHTHERIA CARRIERS: CURE WITH SULPHANILAMIDE. JOAN M. BOISSARD and R. M. FRY, Lancet **1**:610 (May 23) 1942.

Sulfanilamide powder was administered intranasally to 26 children with a heavy bilateral nasal infection (with Corynebacterium diphtheriae and hemolytic streptococci) who had had positive cultures for periods ranging from four to twenty-three weeks. In 24 the nasal infection was abruptly and permanently ended by the first eight day course of treatment. In the other 2 this result was achieved by a second course.

LANGMANN, New York.

Acute Infectious Diseases

ROENTGEN MANIFESTATIONS OF ADULT TOXOPLASMOSIS. L. R. SANTE, Am. J. Roentgenol. **47**:825 (June) 1942.

Toxoplasmosis is a disease produced by Toxoplasma, a protozoan usually classed with the sporozoa. Two cases of the adult type, both with fatal termination are presented, with the roentgenographic and pathologic observations. The essential changes were those of an acute interstitial pneumonitis with associated pulmonary congestion and edema, chiefly localized to the lower lobes. The similarity of the lesions to those of spotted fever, psittacosis and American Q fever is discussed.

SQUIRE, Chicago.

THE USE OF BOVINE ANTITOXIN FOR THE PROPHYLAXIS OF TETANUS. JEROME GLASER, New York State J. Med. **42**:1080 (June 1) 1942.

Since 50 per cent of all the deaths from tetanus in the United States occur in children under 15 years of age, the prophylaxis of tetanus is of especial interest to the pediatrician. While tetanus toxoid is an ideal agent, it is not yet in general use, and it frequently becomes necessary to use tetanus antitoxin. There are a number of severe reactions that occur with tetanus antitoxin. Glaser has used a bovine tetanus antitoxin in 38 cases, the patients ranging from 1½ to 18 years of age, with only 1 instance of serum sickness. As one half of these patients gave a history of allergic disease, this series is a good test of the value of bovine antitoxin.

In 2 of the patients extremely severe reactions had followed small injections of horse serum. For these patients the bovine antitoxin was used successfully, without symptoms. Bovine tetanus antitoxin should be used in cases in which the patient is known to be sensitive to horse serum. When patients are given tests for allergy they should be tested with both equine and bovine serum.

AIKMAN, Rochester, N. Y.

CHEMOTHERAPY OF ACUTE BACILLARY DYSENTERY. GEORGE M. LYON, South. M. J. **35**:606 (June) 1942.

The author reports that early recognition and early institution of therapy are important in the successful treatment of bacillary dysentery. The best results are definitely attained when chemotherapy is applied early in the disease.

Sulfaguanidine is as effective in the treatment of acute bacillary dysentery as sulfanilamide is in the treatment of some streptococcic infections or as others of the sulfonamide compounds are in the pneumococcic infections.

Besides its therapeutic effectiveness, sulfaguanidine is administered with ease, is well tolerated and has a wide margin of safety; hence it is the ideal agent for the treatment of bacillary dysentery.

SCHLUTZ, Chicago.

Chronic Infectious Diseases

CHEMOTHERAPY OF TUBERCULOSIS. GARY ZUCKER, MAX PINNER and HAROLD THOMAS HYMAN, Am. Rev. Tuberc. **45**:292 (March) 1942.

Thirteen patients with tuberculosis were treated with large doses of sulfanilamide to ascertain the practicability of the method rather than for any possible beneficial effect. The

duration of the disease in these patients varied from about six months to fifteen years. Most of the patients had exudative lesions with little or no destruction of tissue, although a few with far advanced fibrocavitary tuberculosis were included.

Sulfanilamide was given in 0.8 per cent solution by intravenous drip. Five successive daily intravenous treatments continuing for ten to eleven hours constituted one course. At the end of the five day period most patients were given moderate doses of sulfanilamide by mouth for from one to three days.

Such a course was repeated in from three weeks to three months if well tolerated and it appeared that beneficial effect might be expected. The total dose for each course varied from 50.2 to 86 Gm. During drip administration it was possible to maintain blood levels between 17 and 32 mg. per hundred cubic centimeters.

Patients undergoing this treatment experienced most of the usual toxic reactions. Nausea and vomiting were less severe, while fever, chilliness and dyspnea occurred more frequently. During the periods of administration of sulfanilamide, fever, increase of cough, sputum and rales, elevated sedimentation rates and leukocytosis were observed in most patients.

No striking or permanent benefits resulted from this treatment. Permanent or complete conversion of sputum was not obtained in any patient. In a few patients mucosal lesions in the pharynx, larynx or bronchi were at least temporarily benefited.

EUGENE SMITH, Ogden, Utah.

PROMIN IN EXPERIMENTAL TUBERCULOSIS. WILLIAM H. FELDMAN, H. CORWIN HINSHAW and HAROLD E. MOSES, Am. Rev. Tuberc. **45**:303 (March) 1942.

The search for a specific treatment for tuberculosis, which had lagged for a number of years, receives new impetus from the development of the newer chemotherapeutic agents. This study of the results of the administration of the drug called "promin" (p,p′-diaminodiphenylsulfone-N,N′-didextrose sulfonate) to guinea pigs with experimental tuberculosis was conducted at the Mayo Foundation, Rochester, Minn. In the first experiment the drug was administered orally with the food, commencing two days before the tubercle bacilli were introduced, while a group of animals similarly inoculated but which did not receive the drug were observed as controls. The animals receiving the promin consumed from 300 to 400 mg. per twenty-four hours. This resulted in a concentration of the drug in the blood of from 2.3 to 4.3 mg. per hundred cubic centimeters. The two facts of importance in the appraisal of the effects of any chemotherapeutic agent in such an experiment are the survival time and the character of the disease process. In this experiment, it was found that at the time when all of the control animals were dead with lesions of progressive tuberculosis in all the organs of predilection 83 per cent of the animals receiving the drug were living. Also in the treated animals it appeared that the disease was less malignant and was unable to exert a lethal effect in the time required for the disease to do so in the untreated animals. Of those that had lesions, the histologic characteristics of the disease process were modified favorably.

In the second experiment promin was administered to groups of animals at periods varying from two days before the day of infection to six weeks after. At the end of six months all of the control animals were dead, while 84 per cent of the treated animals survived; demonstrable lesions of tuberculosis were absent in the liver, lungs and spleen of 57 per cent of the animals receiving promin. It is concluded that under the conditions of the two experiments promin had a deterrent effect on experimental tuberculous infection.

EUGENE SMITH, Ogden, Utah.

APPETITE IN CHILDREN WITH EXTRAPULMONARY TUBERCULOSIS. JOSEPH D. WASSERSUG, Am. Rev. Tuberc. **45**:544 (May) 1942.

The effects of the administration of vitamin B and of insulin to 12 children suffering from extrapulmonary tuberculosis whose ages varied from 5 to 11 years was observed with especial reference to their effect on appetite and weight. Vitamin B was given in the form of yeast by mouth and in the form of thiamine chloride subcutaneously. Insulin was given alone and in conjunction with vitamin B. It appeared from these observations that in the presence of an active tuberculous lesion neither vitamin B nor insulin exerts an appreciable effect on the appetite.

EUGENE SMITH, Ogden, Utah.

TUBERCULOSIS: ITS EVOLUTION AND ITS ERADICATION. C. A. STEWART, South. M. J. **35**: 410 (April) 1942.

The author suggests supplying each household unit with the protection provided by a thorough tuberculosis survey, which includes: (1) the routine application of the tuberculin test

to the entire membership of each household unit for the purpose of identifying the infected and the uninfected members of the group; (2) the clinical laboratory and roentgen studies of the infected tuberculin-sensitive members of each family unit for the purpose of detecting patients with open tuberculosis, and (3) the segregation of patients with open tuberculosis until their disease ceases to be contagious.

SCHLUTZ, Chicago.

PARROT'S PSEUDOPARALYSIS. R. BENOIT, Union méd. du Canada **71**:357 (April) 1942.

A 2 month old infant had not been moving his arms for a week. Movement of his arms or legs caused him pain. There was slight nonsanguineous nasal discharge. Roentgen examination revealed a destructive process in the epiphyses of the long bones of the arms and legs. Wassermann and Kahn reactions of the blood of the baby and of the parents were positive for syphilis.

Antisyphilitic treatment produced clinical and roentgenographic improvement.

DAFFINEE, Boston.

CLINICAL FORMS OF PULMONARY TUBERCULOSIS IN CHILDHOOD. A. CARRAU, Arch. de pediat. d. Uruguay **13**:211 (April) 1942.

The author discusses curable forms of tuberculous condensations which appear as the earliest manifestation of tuberculosis and which generally develop in the neighborhood of parenchymatous foci or as a focus in the mediastinal ganglions. They are generally revealed by roentgen examination. Most of them recede spontaneously. They are commonly observed in infants up to the age of 2 years.

The common forms are: (*a*) perifocal infiltrations; (*b*) perihilar infiltrations; (*c*) infiltrations in the pulmonary fissures, and (*d*) infiltrations in the individual lobes. These infiltrations can develop as acute processes or take on chronic form. It is difficult sometimes to determine the primary or secondary character of the infiltrative lesion by roentgenologic or clinical study. It is difficult to differentiate the trouble from caseous pneumonia or from pulmonary atelectasis.

The prognosis in all of these conditions is generally favorable. The treatment consists in following the general rules laid down for the treatment of tuberculosis in childhood.

SCHLUTZ, Chicago.

ARTERITIS OF THE LARGE VESSELS IN CONGENITAL SYPHILIS OF THE INFANT. C. T. UMANA and R. ATALAYA, Bol. Soc. cubana de pediat. **14**:253 (May) 1942.

Arteritis of the large vessels occurs frequently in the children of Bogota and in the majority of cases is syphilitic in origin. If arteritis is found in the child, syphilis should be checked for by hematologic examination even though there is complete absence of any other syphilitic symptoms.

The authors recommend that antisyphilitic treatment be given even though actual symptoms of syphilis are absent and the examination of the blood discloses no evidence of the disease.

SCHLUTZ, Chicago.

Diseases of Blood, Heart and Blood Vessels and Spleen

THE RATIONALE OF OPERATIVE TREATMENT OF SUBACUTE BACTERIAL ENDARTERITIS SUPERIMPOSED ON PATENT DUCTUS ARTERIOSUS. A. S. W. TOUROFF, Am. Heart J. **23**:847 (June) 1942.

Five patients suffering from bacterial endarteritis complicating patent ductus arteriosus were cured by ligation or division of the ductus. Chemotherapy was not employed.

The author believes that vegetations must be present in the pulmonary artery in cases of infection of the ductus, but he atributes the success of the operation to the facts that the current through the ductus no longer traumatizes the adjacent pulmonary artery, that the pulmonary circulation is more efficient and that relatively few organisms pass through the pulmonary capillaries to enter the peripheral circulation.

GIBSON, Chicago.

SPECIAL SUBSTANCES IN THE URINE OF LEUCEMIA PATIENTS. F. R. MILLER, W. A. HAUSER and H. W. JONES, Proc. Soc. Exper. Biol. & Med. **50**:115 (May) 1942.

The urines of patients with chronic myeloid leukemia were fractionated after extraction with chloroform, and the various fractions were injected into guinea pigs. The alkali-soluble fraction (B) was able to cause cellular proliferation which was reported earlier (Miller,

F. R., et al., *Proc. Soc. Exper. Biol. & Med.* **41**:479, 1939; **45**:387, 1940), whereas the ethyl ether-soluble fraction (A) was unable to effect a change in the tissues. The petroleum ether-soluble fraction (C) caused proliferation of the myeloid cells of the liver, lungs, spleen and adrenals which was more marked than in any of the other animals studied. The proliferation of the lymphoid cells was the same with the three fractions when urine from patients with chronic lymphoid leukemia was injected. The urine from normal patients produced no cellular response in the animals inoculated.

HANSEN, Minneapolis.

ABDOMINAL CRISES IN SICKLE CELL ANEMIA. JULIO G. CABRERA CALDERIN, J. M. LABOURDETTE SCULL and L. BARRERAS, Arch. de med. inf. **11**:61 (April-June) 1942.

The authors present the case of an 11 year old Negro girl who entered the hospital with a diagnosis of an acute condition in the abdomen, which was later found to be the crisis of sickle cell anemia. They stress the point that this condition must always be considered in all abdominal crises of Negroes.

SANFORD, Chicago.

A PHYSICOCHEMICAL STUDY OF THE PRECIPITATION OF SERUM WITH SULFURIC ACID. J. A. TABANERA, F. MODERN and G. RUFF, Rev. Soc. argent. de biol. **18**:106 (May) 1942.

Tabanera has previously drawn attention to the fact that certain serums fail to yield a precipitate when mixed with sulfuric acid in suitable amount. In the present study the authors attempt to explain the phenomenon. They showed that the precipitate gives a positive reaction for amino acids and contains the same amount of nitrogen as proteins. Electrodialyzed serum did not precipitate with the acid. Precipitation occurred after pseudoglobulins from normal serum are added but not after addition of globulins from serums which did not previously form a precipitate, that is, from those which were "positive" in Tabanera's terminology.

MCCUNE, New York.

VARIATIONS IN THE INITIAL AND FINAL COMPLEXES OF THE MYOCARDIAL ELECTROCARDIOGRAM ACCORDING TO THE DIRECTION OF PROPAGATION OF THE STIMULUS. S. R. AMANCHASTEGUI, O. ORIAS and S. A. SEGURA, Rev. Soc. argent. de biol. **18**:138 (May) 1942.

Electrocardiographic records were made of fragments of muscle of various shapes removed from diverse parts of the ventricles of a dog and artificially stimulated. These showed that whereas the orientation of the initial complex, the R wave, depends on the direction of spread of the stimulus, the orientation of the final complex, the T wave, remains unchanged whatever the direction of propagation of the stimulus.

MCCUNE, New York.

Diseases of Nose, Throat and Ear

ROENTGEN THERAPY IN OTITIS MEDIA. L. L. TITCHE and W. E. LAWSON, Am. J. Roentgenol. **47**:764 (May) 1942.

A second series of 52 cases in which otitis media was treated by roentgen therapy with use of 85 kilovolts, 5 milliamperes, 16 inch (40 cm.) target-skin distance and a 1 mm. aluminum filter is presented. The dose was 50 to 60 r for infants, and for young children and adults the dose varied from 60 to 100 r. Therapy was successful in each case, shortening the course by six days in the cases of acute uncomplicated otitis media, and by sixteen days in cases in which there were complications. Thirty-three patients with acute catarrhal otitis media were given one treatment of 79.09 r (average). The drum was normal in an average of three and thirteen hundredths days. In 14 cases of acute purulent otitis media with treatment on the average of one and forty-three hundredths times and with an average dose of 71.23 r, a dry ear was attained in ten and seventy-two hundredths days. In 5 cases of chronic purulent otitis media with an average of one and sixty-eight hundredths treatments and an average dose of 76.49 r a dry ear was attained in fourteen and five hundredths days.

No ill effects have yet been noted in a total of 110 cases thus far reported.

SQUIRE, Chicago.

CARCINOMA OF THE LARYNX IN A GIRL AGED 15. ARTHUR J. CONES, Arch. Otolaryng. **35**:426 (March) 1942.

The case of a 15 year old girl with fatal carcinoma of the larynx is reported. The incidence of juvenile cancer and its highly malignant and fatal aspects are discussed. A careful

laryngeal examination of every child who presents hoarseness as a symptom is stressed. The reader's attention is expressly called to the fact that symptoms which would readily be recognized as malignant in an adult may often be incorrectly diagnosed when they occur in a child or an infant.

GREENWOOD, Chicago.

CHEMOTHERAPY IN ACUTE NONDIPHTHERITIC LARYNGOTRACHEOBRONCHITIS. HERBERT GRAEBNER, Arch. Otolaryng. **35**:523 (April) 1942.

The value of chemotherapeutic measures in the routine treatment of nondiphtheritic croup is discussed, and statistics derived from a comparison of two groups of patients with acute nondiphtheritic laryngotracheobronchitis, one of which received chemotherapy as adjunct treatment, are presented. In anticipation of progressive infection of the tracheobronchial tree sulfapyridine administered orally was used in most cases. A pronounced decrease in the mortality percentage was observed in the group receiving chemotherapy. An analysis of observations indicates the drugs to be ineffective in the presence of certain groups of bacteria and of marked physical exhaustion.

GREENWOOD, Chicago.

INTRACRANIAL COMPLICATIONS OF TONSILLAR ORIGIN WITH SPECIAL REFERENCE TO THEIR INCIDENCE AND PATHOGENESIS. H. J. HARA and CYRIL B. COURVILLE, Arch. Otolaryng. **35**:530 (April) 1942.

The authors report 2 cases of intracranial complications of acute tonsillar infection, having reviewed 25,000 autopsy reports before finding 1 case of the extremely rare involvement. Operative trauma on recent lesions as a contributing factor in causing such complications is discussed.

GREENWOOD, Chicago.

FUSOSPIROCHETAL ORGANISMS AND TONSILLITIS: BISMUTH THERAPY OF TONSILLITIS. JAMES FARRAR LEWIS, Arch. Otolaryng. **35**:587 (April) 1942.

The author presents a report of 9 cases of acute and chronic tonsillitis in which laboratory examination revealed Vincent organisms to be important etiologic factors, indicating these organisms to be considerably more active than generally presumed. The use of bismuth is advocated as a highly effective form of treatment in cases of severe tonsillitis.

GREENWOOD, Chicago.

CONGENITAL ATRESIA OF THE POSTERIOR NARES: REPORT OF TWO CASES. ALFRED A. SCHWARTZ and HAROLD J. ISAACS, Arch. Otolaryng. **35**:603 (April) 1942.

The authors report 2 cases of congenital atresia of the posterior choanae in adults and describe the necessitated surgical procedure. It is suggested that obstructive cicatrices may be avoided if the entire occluding membrane can be removed.

GREENWOOD, Chicago.

OTITIS MEDIA AND MASTOIDITIS IN CHILDREN: BACTERIOLOGIC STUDIES WITH SPECIAL REFERENCE TO THE PATHOGENICITY OF STAPHYLOCOCCI. E. NETER, F. NEUBURGER and M. L. SHORT, Arch. Otolaryng. **35**:631 (April) 1942.

The results of a bacteriologic survey of cases of mastoiditis and otitis media to determine the relative pathogenicity of staphylococci are presented. Laboratory evidence revealing the organism to be of significance in 36 per cent of 438 cases of otitis media and in only 1 per cent of 106 cases of mastoiditis is discussed.

GREENWOOD, Chicago.

TONSILS AND ADENOIDS: SUMMARIES OF THE AMERICAN AND BRITISH BIBLIOGRAPHIC MATERIAL AVAILABLE IN THE FIELD OF OTOLARYNGOLOGY. J. DUDLY SINGLETON, Arch. Otolaryng. **35**:653 (April) 1942.

An interesting and comprehensive review of American and English literature for the years 1940 and 1941 on the subject of tonsils and adenoids is made, and attention is called to several noteworthy articles.

GREENWOOD, Chicago.

STUDIES ON PUPILS OF THE PENNSYLVANIA SCHOOL FOR THE DEAF: IV. MECHANISM OF INHERITANCE OF DEAFNESS. WALTER HUGHSON, ANTONIO CIOCCO and C. E. PALMER, Arch. Otolaryng. **35**:871 (June) 1942.

A comprehensive investigation into the hereditary factors and their possible relation to the auditory impairment of 307 of the 535 pupils in the Pennsylvania School for the Deaf is

reported on by the author. Results of this analysis would seem to indicate that differentiation between children whose deafness is inherited and those whose deafness is acquired can be made from the history at the onset and the immediate cause. This survey further indicates that the deafness is transmitted according to the mendelian pattern involving a single recessive gene. Environmental conditions are strongly stressed as contributing factors.

GREENWOOD, Chicago.

TONSILLECTOMY AND ITS EFFECT ON THE SINGING VOICE. WILLIAM A. C. ZERFFI, Arch. Otolaryng. **35**:915 (June) 1942.

Zerffi discusses the impairment of the singing voice following tonsillectomy, despite improved technic. The necessity for a better understanding by both the singer and the laryngologist of the action of the palatal muscles and the reeducation of these muscles after surgical intervention is particularly stressed.

GREENWOOD, Chicago.

ADAMANTINOMA OF THE FLOOR OF THE RIGHT NOSTRIL: OCCURRENCE IN A CHILD AGED FIVE YEARS. ALFRED B. BERKOVE, Arch. Otolaryng. **35**:928 (June) 1942.

The author reports a case of adamantinoma in a 5 year old girl. The neoplasm was removed with a margin of what appeared to be normal tissue, and the child was given high voltage roentgen radiation in an amount consistent with her age.

GREENWOOD, Chicago.

STUDIES OF PUPILS OF THE PENNSYLVANIA SCHOOL FOR THE DEAF: III. AN ANALYSIS OF SPEECH CHARACTERISTICS IN DEAFENED CHILDREN WITH OBSERVATIONS ON TRAINING METHODS. WALTER HUGHSON, ANTONIO CIOCCO, E. G. WITTING and P. S. LAWRENCE, Child Development **13**:131 (June) 1942.

"Hughson and his associates, working at the Pennsylvania School for the Deaf, have recorded by electrical transcription, the articulated speech of over 350 deafened children. By means of repeated playing back of the resulting records the detailed characteristics of the speech of each of the children was analyzed and the data presented in statistical terms. It is believed that the method is unique and one that merits further exploration.

"The authors have pointed their analysis so as to bring out with especial clarity the differences resulting from the training histories of the children. It is evident from Hughson's material that auricular training produces a much more favorable result than does the older 'oral' method. The latter fact is especially striking in cases where the method has been started early and continued for as long as 4 to 5 years." [AUTHORS' SUMMARY]

VITAMIN D IN VERNAL CATARRH. ARTHUR ALEXANDER KNAPP, J. Allergy **13**:407 (May) 1942.

The author believes that vernal catarrh may be due to a disturbance of the metabolism of vitamin D, calcium and phosphorus.

The daily administration of large doses of vitamin D in the form of viosterol, a minimum of 13,860 units, and calcium and phosphorus in the form of mineral mixture tablets (calcium, 140 mg.; phosphorus, 83 mg.; iron, 1 mg.; copper, 0.05 mg.; magnesium, 2.8 mg.; sodium, 5 mg., and potassium, 5 mg. per tablet) produced an improvement in the symptoms of lacrimation, photophobia and itching, and in blepharospasm and conjunctival injection. Dosage of the mineral tablets was gaged by the intake of milk: If a patient drank 1 quart (1 liter) of milk daily, 1 tablet was prescribed; for each glass less than a quart, 2 tablets were added.

HOYER, Cincinnati.

CHRONIC CORYZA AND VITAMINS. ALFREDO VIDAL FREYRE, An. Soc. puericult. Buenos Aires **8**:160, 1942.

The frequent observation of children who catch cold in spite of every effort to avoid it led to this work. The author used a preparation of vitamin A, 5 drops three times a day, in each nasal fossa.

The results were favorable in 17 cases; 8 patients were cured; 4 were much better; 2 showed fair improvement, and 3 were not benefited.

The author explains the favorable results as due to the protective action of vitamin A on the mucous membrane.

It is clear that before treating chronic coryza the proper diagnosis must be made; it would be ridiculous to treat diphtheria, tuberculosis or syphilis with vitamin A.

GIFFEN, Toledo, Ohio.

Diseases of Lungs, Pleura and Mediastinum

ATELECTASIS FOLLOWING PNEUMONIA IN CHILDREN. GEORGE M. WATT, Am. J. Roentgenol. **47**:864 (June) 1942.

The findings in 26 cases of atelectasis following pneumonia in a group of 135 patients are given. The patients were from 3 weeks to 10 years old. This atelectasis may involve all or only part of one or more lobes.

Roentgenograms of lungs with atelectasis showed an increased density of the involved lung plus three additional signs: increased density with displacement of adjacent structures toward the collapsed area; diminution in size of a lobe of the lung by displacement of the interlobar septum toward an area of increased density, and a curvilinear triangle of increased density within a lobe with the base of the triangle at the periphery and the apex directed toward the hilus, indicating atelectasis of one or more bronchopulmonary segments within a lobe. A lateral view of the chest is valuable in detecting small areas of atelectasis.

SQUIRE, Chicago.

COMPLEMENT ACTIVITY IN PNEUMONIA. DAVID D. RUTSTEIN and WILLIAM H. WALKER, J. Clin. Investigation **21**:347 (May) 1942.

The blood serum of apparently healthy persons had remarkably constant hemolytic complement activity within a comparatively narrow range. At the time of admission to the hospital, the blood serum of one sixth of the patients with pneumonia studied had low complement activity. No correlation could be found between complement activity and age, sex, bacteremia or alcoholism. Low complement activity was not found in patients recovering from pneumonia. Complement activity could not be used as an index of prognosis at the time of admission to the hospital in this series of patients with pneumonia, but there was a tendency for the activity to diminish in the period prior to death. GUEST, Cincinnati.

PULMONARY FUNCTION AFTER PNEUMONECTOMY IN CHILDREN. CHARLES W. LESTER, ANDRE COURNAND and R. L. RILEY, J. Thoracic Surg. **11**:529 (June) 1942.

Pulmonary function of 3 children who had undergone pneumonectomy was studied from one to three years after they resumed normal physical activity. This was compared with that of normal children with corresponding physical characteristics.

It was found that the chief difference between the 3 children who had undergone pneumonectomy and the normal subjects was the constant reduction in their breathing reserves in various states of activity. The gas exchange in the normal and in the pneumonectomized children was strikingly similar.

In the child whose postoperative course was the least complicated, the mediastinum became less fixed than in the remaining 2. Overdistention of the lung followed, with lowering of the vital capacity and reduction in maximum breathing capacity. This is the change seen to occur in pneumonectomized puppies. This unfavorable situation is not always anatomically controllable in children and is not physiologically desirable.

DORSEY, Chicago.

A STUDY CONCERNING CLINICAL AND ANATOMIC FEATURES OF REEXPANDED LUNGS WHICH HAD BEEN COLLAPSED BY PNEUMOTHORAX FOR VARIABLE PERIODS OF TIME. B. P. POTTER, J. Thoracic Surg. **11**:554 (June) 1942.

The author deals with the results of observations on 118 patients. Most of them had had cavernous tuberculous lesions for which pneumothorax had been done and reexpansion had been present for from one to eight years.

The complications encountered are discussed. Pleural effusion into the costophrenic sinuses occurred in every patient. Only 70 per cent had large effusions. There were 5 with tuberculous empyemas. Unilateral collapse caused lesions to occur in the other lung very infrequently. It was found that reactivation on reexpansion occurred much less frequently when collapse was maintained for an adequate period of time. In general, it is stated that reactivation occurred much more frequently when the collapse lasted less than eighteen months than when continued longer. Reexpansion occurred in the vast majority of the 118 patients without supplementary surgery. Three needed interruption of the phrenic nerve.

DORSEY, Chicago.

GROWTH OF THE LUNG IN HEALTHY AND SICK INFANTS. STEFAN ENGEL, Arch. Dis. Childhood **17**:41 (March) 1942.

The lung of the normal infant grows fastest in the first months. It doubles its volume in the first three to four months and quadruples it by the end of the first year.

The growth of the lung reacts in infancy to the slightest change, positive as well as negative, of the general condition, and comes to an almost complete standstill in wasting infants. This implies not only that the lung remains small but that the structural differentiation of the tissue is arrested at an early stage.

The arrest of growth and differentiation of the lung explains the high rate of collapse and pneumonia in wasting infants. On the other hand, recognition of the pulmonary impairment suggests that respiratory therapeutics may be an additional aid in the treatment of wasting infants.

KELLY, Milwaukee.

PNEUMONIA IN THE VERY YOUNG INFANT. C. PENICHET, Bol. Soc. cubana de pediat. **14**:188 (April) 1942.

The author reports the results of his experience in 84 cases. He points out the gravity of pneumonia in a very young infant and the comparatively unsatisfactory treatment until the advent of the sulfonamide compounds.

With proper and scientific use of these drugs the mortality from pneumonia has been remarkably lowered and the prognosis greatly improved.

SCHLUTZ, Chicago.

BRONCHIAL PNEUMONIA IN THE VERY YOUNG INFANT. G. C. PENICHET, Bol. Soc. cubana de pediat. **14**:197 (April) 1942.

The author reports on a study of 98 cases of bronchial pneumonia in infants ranging in age from 4 to 12 months. The larger number of cases occurred in the spring and fall months, during April and September.

Primary forms occurred mostly before the sixth month of life. Those in which pneumonia was a complication followed measles, gastroenteritis and whooping cough in the order of frequency mentioned.

Pneumococci, staphylococci, influenza organisms (Haemophilus influenzae), streptococci and micrococci (Micrococcus tetragenus) were the different organisms found. Fever and symptoms referable to the respiratory tract were the most frequent clinical findings, and a large number of the infants had gastrointestinal and neurologic symptoms.

The mortality was highest in the first six months. The athreptic infants and infants with capillary bronchitis showed the highest mortality. The nutritional state of most of the patients was usually poor. The highest mortality was in the dystrophic and premature infants. Purulent pleurisy was the most frequent complication. Other complications were suppurative otitis media, anemia and purulent meningitis.

In the cases in which there was no specific treatment the mortality was 68 per cent. In cases in which serums or vaccine were used and in those with treatment by means of a sulfonamide compound the mortality ranged from 50 to 57 per cent. It was lowered to 40 per cent in cases in which sulfanilamide was exclusively used, in spite of the fact that in many of these cases the patient's condition was most grave.

SCHLUTZ, Chicago.

SULFATHIAZOLE IN TREATMENT OF PNEUMONIA IN THE CHILD. G. GOMEZ CARDENAS, Rev. mex. de pediat. **12**:183 (April 10) 1942.

Sulfathiazole is capable of causing a prompt symptomatic crisis, similar to a natural crisis in pneumonia. Often the temperature descends to normal or nearly normal. The toxicity diminishes and disappears within a few days. Dyspnea grows rapidly better, and the child seems improved. In many cases the temperature is within normal limits after the second day of treatment; at the same time the appetite is restored, and the child is little disturbed. The signs on auscultation improve rapidly in almost all cases, and roentgenograms show marked resolution of the affected portion of the lung.

Toxic reactions produced in children by the medication are slight as a rule, but at times the medication must be suspended. Disturbances are less than those caused by sulfanilamide or sulfapyridine. Also this drug seems to have no unfavorable action on the red cells or on the hemoglobin. The white blood cell count rapidly descends to normal after the first few days of treatment.

As sulfathiazole is more soluble in an alkaline solution, an alkali, such as sodium bicarbonate, should be given to avoid concentration of crystals in the urinary tract. Water should be freely given.

GIFFEN, Toledo, Ohio.

PULMONARY AGENESIS. A. CASTELLANOS, R. PEREIRAS and A. DELGADO, Bol. Soc. cubana de pediat. **14**:268 (June) 1942.

The authors report 3 cases of this exceedingly rare condition. Only 56 cases are reported in the world literature. In only 6 of the cases was the condition recognized in life; in all of the others it was established at autopsy.

The authors describe in considerable detail the diagnostic and exploratory methods used in determining pulmonary agenesis and differentiate it from other pathologic conditions of the lungs. In addition to the roentgenographic study the most valuable procedures are: bronchography, diagnostic pneumothorax, roentgen kymography, angiocardiography (as particularly advised by Drs. Castellanos and Pereiras) and esophagraphy.

Two of the patients whose cases are reported by the authors are alive, 1 a white girl aged 10 years and the other a Negro girl also aged 10. The third patient lived twenty-one days after birth.

The authors give an exhaustive discussion of this rare condition and give visual illustrations of it by a number of excellent roentgenograms and photographic reproduction of pathologic material.

The conditions likely to be found in patients with this condition are: (*a*) a total bronchopulmonary aplasia; (*b*) a bronchial hypoplasia with alveolar aplasia, or (*c*) a bronchoalveolar hypoplasia.

SCHLUTZ, Chicago.

THE TECHNIC OF COLLECTING SAMPLES OF ALVEOLAR AIR. A. D. MARENZI and M. A. COSTOYA, Rev. Soc. argent. de biol. **18**:122 (May) 1942.

The best conditions for obtaining samples of alveolar air have been investigated by use of the Henderson-Morris technic. Time was controlled during the emission of expired air. The subjects were maintained at rest and seated. Using tubes of different capacities the authors found that the carbon dioxide concentration diminishes when the capacity of the tube increases. Barometric pressure has no influence. The relation between the carbon dioxide of the alveolar air and the time of emission of the sample in seconds gives a paraboliform curve. This curve might be considered as formed by two straight lines. By graphic extrapolation the value of carbon dioxide at zero time can be calculated. This corresponds to the carbon dioxide concentration of an instantaneous expiration of no physiologic significance. If the duration in seconds of the respiratory cycle is known, the "effective alveolar air" can be calculated. The curve may be obtained with only one experimental value by use of the equation to the straight line. The impossibility of comparing the values of carbon dioxide of effective alveolar air and the values obtained by tonometry is discussed.

The technic has the following advantages: (1) The effective alveolar air is in accordance with the physiologic cycle of respiration. (2) No special training of the subject is necessary for obtaining the sample; only the exact control of sampling time is important.

McCUNE, New York.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

APPENDICITIS IN INFANTS AND CHILDREN. GROVER C. PENBERTHY, CLIFFORD D. BENSON and CHARLES N. WELLER, Ann. Surg. **115**:945 (June) 1942.

This study represents a review of 1,653 cases of appendicitis in infants and children occurring in a fifteen year period (1927 to 1941). It emphasizes certain facts: (1) that there is a progressive increase in the incidence of appendicitis in children up to 10 years of age; (2) that in cases of appendicitis in children there has been as a rule repeated administration of some type of cathartic; (3) that delay in seeking proper medical attention has tended to complicate the surgical management.

Pain is recorded as the outstanding subjective symptom, accompanied by nausea and vomiting, although the latter may not be present. Fever is found in the majority of cases. The preoperative management is particularly important and is discussed. Chemotherapy for a limited number of patients has proved of definite benefit as an adjunct to the usual routine treatment.

BANTIN, Omaha.

LATENT LIVER DISEASE IN PERSONS RECOVERED FROM CATARRHAL JAUNDICE AND IN OTHERWISE NORMAL MEDICAL STUDENTS AS REVEALED BY THE BILIRUBIN EXCRETION TEST. ARTHUR KORNBERG, J. Clin. Investigation **21**:299 (May) 1942.

The bilirubin excretion test used as a test of hepatic function in a large group of presumably normal persons and in others known to have had catarrhal jaundice led to the following conclusions: (1) Persons long recovered from catarrhal jaundice show an abnormal reten-

tion of bilirubin and a considerable percentage of them have symptoms of hepatic dysfunction; (2) chronic nonhemolytic jaundice occurs in otherwise healthy young persons much more frequently than has been commonly recognized. Presumably normal persons have basal bilirubin values which fall within a narrow range and excrete intravenously injected bilirubin in a relatively uniform way.

GUEST, Cincinnati.

A STATISTICAL STUDY OF SIX HUNDRED AND SEVENTY-ONE CASES OF APPENDICEAL PERITONITIS: PART II. TWO HUNDRED AND TWENTY-SEVEN CASES WITH PALPABLE MASS ON ADMISSION TO THE HOSPITAL. HENRY H. FAXON and HORATIO ROGERS, New England J. Med. **226**:745 (May 7) 1942.

The "Introduction" and "Part I" of this paper appeared in the April 30 issue of this journal. Both parts are very detailed statistical studies and should be read in the original. "Part II" is an analysis of the cases of patients with a palpable mass admitted to the Massachusetts General Hospital during the years 1929 to 1939 inclusive.

Although in nearly half (46 per cent) of these cases the peritonitis occurred between the ages of 15 and 50 years, there was but a single death in this group, whereas in patients under 15 there was a mortality of 9.6 per cent, and over the age of 50 it reached 16 per cent. It is apparent in 56 cases that operation for appendicitis with an associated mass within the first four days of the disease is attended with a low mortality (3.1 per cent). This is in striking contrast to a 12.5 per cent mortality in patients with ruptured appendix without mass formation operated on within this same period. In the forty-eight hour period of the fifth and sixth days of the disease, there was an abrupt and startling rise in the death rate—to 17.4 per cent.

It is therefore apparent that when a mass is present operation done on or before the fourth or after the twelfth day is a relatively safe procedure, with but a 3 per cent mortality. Surgical intervention carried out on the fifth, sixth or seventh day of the illness, however, is especially hazardous, accounting for nearly half (7) the deaths, although only one fifth (21 per cent) of the patients were operated on at that time.

Incision and drainage alone as the original surgical procedure was carried out in 118 cases, with a mortality of 6 per cent. In the significantly large number of cases in which operation was performed after the seventh day (120 cases) removal of the appendix as the original procedure nearly doubled the operative mortality, increasing it from 4 to 7 per cent.

There were no fatalities in the 76 explorations done as a secondary procedure following incision and drainage of the peritoneal cavity.

Appendectomy should be carried out within six weeks after incision and drainage unless the patient is in generally poor condition or some complication provides an indication for a longer interval between operations.

GENGENBACH, Denver.

POLYPS OF THE RECTUM AND COLON. JOHN C. M. BRUST, New York State J. Med. **42**:973 (May 15) 1942.

In complete sigmoidoscopic examination of 2,146 patients polyps were found in 123. Of these patients 18 were children. Since a polyp may become malignant, it should be carefully removed by fulguration and a careful pathologic examination made for malignant changes. Thorough removal and careful follow-up of these patients give good results.

In the discussion, A. M. Buda reported that he had found that 27 per cent of polyps occur in the first decade of life.

AIKMAN, Rochester, N. Y.

SPONTANEOUS PNEUMOMEDIASTINUM (MEDIASTINAL EMPHYSEMA) WITH REPORTS OF TWO CASES IN INFANTS. J. F. BOWSER, Radiology **38**:314 (March) 1942.

Interstitial emphysema may be caused by distention of the lungs produced by forceful muscular effort with the glottis closed. It has been observed in newborn infants following attempts at resuscitation and in children after paroxysms of coughing. It may also develop during childbirth and after lifting heavy objects. It occurs spontaneously, without a history of trauma or unusual pulmonary distention.

Air escaping into the interstitial tissues may give no symptoms or only produce localized pain. If a large amount of air escapes, it may form a subpleural bleb or find its way into the mediastinum. Symptoms may simulate coronary occlusion. There is absence of shock and myocardial weakness. A distinctive sign of mediastinal emphysema is a peculiar crunching, crackling, bubbling sound heard over the heart with each contraction due to compression of the air-filled mediastinal tissue lying between the heart and the anterior wall of the chest. The diagnosis is assured by the appearance of air in the subcutaneous tissues of the neck. Pneumothorax is not a rare complication.

The normal anatomic structure of the mediastinal space consists of an upper and a lower portion. These are divided by the upper level of the pericardium. The lower portion is subdivided into an anterior, middle and posterior mediastinum.

The air escapes through multiple small ruptures in the alveolar bases overlying the finer ramifications of the pulmonary blood vessels. Air-tunneled vascular sheaths are formed. Injuries and diseases of the lungs, larynx, trachea or bronchi may account for the mediastinal emphysema and for the presence of foreign bodies. The outstanding effect is a mechanical interference with the circulation by compression of the large veins entering both sides of the heart.

Symptoms are extreme cyanosis and dyspnea, rapid pulse, congestion of the superficial veins of the neck and low blood pressure. Subcutaneous emphysema is usually present.

The authors report 2 instances of mediastinal air in newborn infants demonstrated by roentgenograms in the anterioposterior projection and in the lateral projection. The condition of 1 child was relieved by the introduction of a needle under the sternum in the fourth anterior space on the right. The escaping air forced the plunger out of the syringe. In the other the condition was not treated but the child recovered completely in three days.

In infants particularly, the combination of persistent dyspnea with signs of increasing circulatory embarrassment warrants consideration of the possibility of pneumomediastinum, and relief of mediastinal pressure may be life saving. Roentgenograms of the chest, particularly in the lateral projection, are diagnostic.

ANSPACH, Chicago.

MECKEL'S DIVERTICULUM. ALFRED LEDOUX, Radiology **38**:728 (June) 1942.

Positive roentgenologic diagnosis of Meckel's diverticulum has been infrequent. The author was able to identify barium in a diverticulum of a 2½ year old child on films made four and five hours after the ingestion of barium. Surgical removal and pathologic study showed the lesion to be the cause of the signs and symptoms.

The symptoms of the onset were those of a feeling of weakness, accompanied by nausea and vomiting. The vomitus consisted of undigested food which had been eaten some hours previously. Following the vomiting there was a copious watery bowel movement containing blood, both bright red and dark. There was an earlier history of vague abdominal pain on occasions. Physical examination revealed no abnormalities.

Three days after the first attack there was another, but it was not accompanied by vomiting. In this interim the stools had been black, but now bright red blood was seen again. Physical examination still showed nothing unusual, and a roentgen examination of the colon at this time revealed no abnormalities.

Three days later a barium sulfate meal was given, and four hours later an extraluminal shadow of barium was seen at the level of the promontory of the sacrum. This shadow was 1 cm. in diameter and was movable and tender. The same shadow was seen on a film taken five hours after the barium meal.

After eighteen days of symptomatic treatment there was still evidence of bleeding from the gastrointestinal tract. A laparotomy was performed, and a diverticulum with a lumen 12 mm. in diameter along with a portion of the ileum was removed.

The pathologic report was Meckel's diverticulum with superficial necrosis of the gastric mucosa in the wall of the diverticulum. Recovery was uneventful.

ANSPACH, Chicago.

HYPERTROPHIC PYLORIC STENOSIS. J.-B. BOMBARDIER, Union méd. du Canada **71**:589 (June) 1942.

The author reports a typical case of hypertrophic pyloric stenosis cured by operation. He points out the success reported by Scandinavian authors using medical treatment with atropine methylnitrate. This drug, fifty times less toxic than atropine, is used in a 1 per cent alcoholic solution. The preparation is absorbed directly by the buccal mucosa; thus loss by vomiting is avoided. The dose is begun at 1 drop a day and increased by 1 drop every day until vomiting is ameliorated. Ordinarily no more than 5 drops daily is required. Toxicity is manifested by flushing of the face.

DAFFINER, Melrose, Mass.

PEPTIC ULCER IN INFANCY AND CHILDHOOD WITH A REVIEW OF THE LITERATURE. KATHARINE J. GUTHRIE, Arch. Dis. Childhood **17**:82 (June) 1942.

This is a review of 9 cases of peptic ulcer in infants, all except 1 under 6 months of age.

Clinically, hemorrhage from the stomach or bowel is the most characteristic sign of peptic ulceration in young children. Hemorrhage may be the initial feature, or it may be preceded by dyspepsia. The child may collapse in the course of an apparently simple gastroenteritis

and die from concealed hemorrhage, or the lesion may remain clinically latent till perforation and peritonitis supervene. In the absence of hemorrhage, ulcer is generally unsuspected.

KELLY, Milwaukee.

NON-ROTATION OF THE GUT. P. D. MUKERJI and S. P. GUPTA, J. Indian M. A. **11**:195 (April) 1942.

The authors report on (without the clinical history) and discuss a case of intestinal malrotation in which the interference occurred during the second stage of rotation. The whole of the small intestine was situated in the right lumbar and right iliac regions, and the whole of the large intestine was situated on the left side of the same regions. The small intestine hung free within the right part of the abdominal cavity, attached only by a small root to the posterior abdominal wall in the region of the pancreas. The superior mesenteric artery passed down in front of the root of the loop of jejunum, which was attached by adhesions to the anterior surface of the second part of the duodenum and also to the posterior abdominal wall below it.

GONCE, Madison, Wis.

TREATMENT OF INFECTIVE DIARRHOEAS IN CHILDREN WITH SULFAPYRIDINE AND BANANA PULP. B. COELHO, J. Indian M. A. **11**:269 (June) 1942.

Thirty-five patients with dysentery and 65 with ordinary diarrhea were treated with sulfapyridine (¾ to 1 grain per pound [0.05 to 0.065 Gm. per kilogram] per day), ripe banana pulp (2 ounces per pound [113 Gm. per kilogram] per day) and weak tea; milk was added to the diet after forty-eight hours. Fifty-eight improved in forty-eight hours and 84 were well in four days. Only 7 died, and of these 6 within twenty-four hours of admission to the hospital.

GONCE, Madison, Wis.

CONGENITAL ATRESIA OF THE COLON. VICTOR SANTAMARINA, CARBONELL SALAZAR and D. SOSA BENS Y HECHEVARRIA, Arch. de med. inf. **11**:47 (April-June) 1942.

In the case of atresia of the colon here reported diagnosis was made at birth and operation was performed at 4 days of life. In a review of the literature the authors find that atresia of the colon is a rare anomaly of intestinal structure and that the termination is almost always fatal, even with early operation.

SANFORD, Chicago.

INTUSSUSCEPTION IN AN INFANT TREATED WITH BARIUM ENEMA. MAURICIO LITMANOVITCH. Rev. méd. munic. **3**:411 (April) 1942.

A 10 year old child suffered from an intussusception of sixteen hours' duration at the level of the transverse colon, as shown by a roentgenogram. This was reduced by an opaque barium sulfate enema, as shown by two later roentgenograms.

SANFORD, Chicago.

THE SYNDROME OF VON GIERKE (GLYCOGENESIS). JEAN MURY, Ann. pædiat. **158**:177, 1942.

"Two observations of cases of von Gierke's disease not published so far offered the opportunity for the study of this syndrome. Emphasis is laid on the importance of the secondary symptoms, which are dependent on the disturbance of metabolism. Their frequency and inconstancy point to the pathogenesis. As other authors have stated, this syndrome is hypophysarily-diencephalically conditioned. There are hepatomegalia of unknown origin, the separation of which from the von Gierke's disease may cause difficulties in diagnosis. Description of a von Gierke syndrome in the course of a diabetes juvenilis and the importance of this occurrence for the study of the pathogenesis of the von Gierke syndrome is shown."

[EDITOR'S SUMMARY]

Nervous Diseases

CALCIFIED TUBERCULOMA OF THE BRAIN. LAURENCE M. WEINBERGER and FRANCIS C. GRANT, Am. J. Roentgenol. **47**:525 (April) 1942.

The authors report a case, in which diagnosis was made preoperatively, as the nineteenth verified case of calcified tuberculoma. The incidence is about 1.01 per cent of all intracranial tumors. The patient, a Negro boy about 12 years old, had a history of frequent epileptiform, and later jacksonian, convulsions affecting the left arm and leg since the age of 5 years, with weakness and shortening of the parts. He had a slightly hemiplegic gait and walked on the left toes. A physical examination was essentially noncontributory save for increased tendon reflexes on the left and a large calcified tracheobronchial lymph node in the hilus of the right lung. Examination of the skull showed a well localized area of spongy calcification in the right parieto-occipital region just beneath the dura. The patient was discharged,

though still under observation, and was reentered two and a half years later. He had a history of aura preceding recent jacksonian attacks with weakness on the left side, convulsions and unconsciousness. He was hyperactive, giggling and dull. The left leg was 3 cm. shorter and the left arm 2 cm. shorter than the right. An operation revealed a stony mass high in the parietal lobe, densely adherent, avascular, blending with the cortex of the brain. The specimen weighed 65 Gm. and measured 3 by 2 by 4 inches (7.6 by 5 by 10.2 cm.).

Decalcified sections showed conglomerate tuberculoma. The calcareous shell seen on the roentgenogram was in the center of the mass and was surrounded by a hyalinized zone equal in size. The patient recovered with paralysis of the left arm and loss of cutaneous sensibility on the left side. Improvement was slow.

The lesions were chronic, ranging in other reported cases from four to sixty-one years' duration. Calcification occurs at the junction of the zones of necrotic tissue and connective tissue, enclosing the necrotic core in a calcium shell which is surrounded by hyalinized connective tissue.

Roentgenograms vary with thickness of shell, which is nearly equal in all dimensions although irregular and of varying density. The location in 18 cases was near the inner table of the calvarium. The peripheral calcified zone of the tuberculoma may be large, the calcified areas being 0.2 to 3.5 cm. in diameter.

Differential diagnosis included calcified hemorrhage and abscess. Clinical history will sometimes aid in differential diagnosis.

SQUIRE, Chicago.

TOXOPLASMIC ENCEPHALOMYELITIS. CORNELIUS G. DYKE, ABNER WOLF, DAVID COWEN, BERYL H. PAGE and JOHN CAFFEY, Am. J. Roentgenol. **47**:830 (June) 1942.

Toxoplasmosis is a disease due to a protozoan parasite frequently affecting the central nervous system. Clinical features are given, including the presence of miliary granulomas scattered throughout the central nervous system. The source may be rodents and birds. Intrauterine infection has been established in some cases of infantile toxoplasmosis.

Roentgenographic findings and brief histories are given of cases of the infantile, or congenital, form. Diffuse intracerebral calcification appears to be the most striking roentgenographic evidence of this form, occurring in small patches about 2 mm. in diameter or in streaks, particularly in the basal ganglia or thalami. Internal hydrocephalus is also a feature. Pneumonitis similar to inflammatory or telectatic lesions found in infants may occur.

An excellent discussion is appended.

SQUIRE, Chicago.

SULFONAMIDES: PASSAGE INTO SPINAL FLUID AND RECTAL ABSORPTION. WINDSOR C. CUTTING and ERNEST H. SULTAN, Ann. Int. Med. **16**:708 (April) 1942.

Sulfapyridine and sulfanilamide permeate the meninges and produce higher concentrations in the spinal fluid than does sulfathiazole. The spinal fluid levels approach those present in the blood. The rectal absorption of sulfapyridine and sulfathiazole is practically nonexistent. Rectal absorption of sulfanilamide is considerable and may suffice when low blood concentrations are sufficient for therapeutic effects.

READING, Galveston, Texas.

FATAL INFECTIOUS POLYNEURITIS IN CHILDHOOD: INFECTIOUS NEURONITIS, ACUTE POLYNEURITIS WITH FACIAL DIPLEGIA, GUILLAIN-BARRÉ SYNDROME AND LANDRY'S PARALYSIS. CHARLES D. ARING and ALBERT B. SABIN, Arch. Neurol. & Psychiat. **47**:938 (June) 1942.

The authors reported a case of fatal polyneuritis in a boy 4½ years of age. Although the spinal fluid was not examined, the postmortem microscopic picture was typical of the disease.

BEVERLY, Chicago.

EPIDEMIOLOGY OF ENCEPHALITIS; WESTERN EQUINE TYPE, MANITOBA, 1941. C. R. DONOVAN and M. BOWMAN, Canad. M. A. J. **46**:525 (June) 1942.

This is a brief report on encephalitis in Manitoba from 1938 to 1941.

During four years serologic reactions have been reported positive for western equine virus in 82 cases, for St. Louis virus in 1 and for Japanese B virus in 1. The 1941 cases were distributed widely throughout the province and occurred mostly during August; 70 per cent were among males; 81 per cent of all patients were 20 years of age and older.

There were 78 deaths, giving a case fatality rate of 15.3 per cent.

There is no evidence that spread from person to person was a factor in this epidemic. The disease may be insect borne.

MOORE, Omaha.

THE OCCURRENCE OF UNILATERAL (JACKSONIAN) GRAND MAL SEIZURES IN TETANY. J. M. MEREDITH, J. Nerv. & Ment. Dis. **95**:405 (April) 1942.

Meredith states that only 3 instances of unilateral convulsions due to tetany have been recorded. He reports the case of a 3 year old Negro boy who had severe clonic convulsive seizures on the right side, with complete loss of consciousness. Studies of the calcium and phosphorus of the blood and the presence of Erb's sign established the diagnosis of tetany and rickets, and there was prompt improvement after treatment with calcium gluconate and viosterol. Follow-up studies showed no recurrence, although a suggestive Erb sign forty-nine months later indicated subclinical tetany.

The early clinical picture was similar to that seen with a mass intracerebral lesion, and it is suggested that tetany be considered in the differential diagnosis of similar conditions. The author believes that a reading of less than +5 milliamperes in the cathodal closing contraction with the galvanic current in a child under 5 years of age is suggestive of low diffusible calcium in the tissues and establishes the diagnosis of tetany. He emphasizes the fact that Erb's phenomenon is the most persistent and reliable sign of spasmophilia and the last to disappear. Certain cases of so-called idiopathic epilepsy in children may actually be instances of tetany with an average blood calcium but a lowered tissue (ionized) calcium content.

CHODOFF, Washington, D. C. [ARCH. NEUROL. & PSYCHIAT.]

SOME REMARKS ON TUMORS OF THE BRAIN IN CHILDHOOD. OTTO MARBURG, J. Nerv. & Ment. Dis. **95**:446 (April) 1942.

From a review of the statistics of various authors, Marburg concludes that 14 to 15 per cent of all tumors of the brain occur in childhood. There are an increase in the number of cases from the first to the sixth year and a drop at the seventh year, this level being approximately maintained thereafter. Fifty to 60 per cent of the tumors are subtentorial, and about 30 per cent occur in the diencephalic region. Some cerebellar cysts and cystic astrocytomas are dysraphic, depending on disturbance of the closure lines of the neural tube. Others, such as tumors of the craniopharyngeal duct, cysts of Rathke's pouch and pineal and infundibular neoplasms, may be considered as diverticular tumors. A third group comprises the tumors of transformation, such as those originating in the posterior velum.

Tumors of the hypophysis and the pineal gland are characterized principally by growth disturbances of various types. The existence of acromegaly in childhood has not been proved conclusively, although the transitory acromegaly of adolescence is recognized. Pubertas praecox occurs only in persons with complete destruction of the pineal gland before the age of 7. With destruction developing later, there occurs premature development of secondary sex characters. Tumors of the quadrigeminal plate may cause Nothnagel's syndrome—bilateral incomplete oculomotor palsy followed by ataxia. Tumors within the third ventricle cause symptoms similar to those of hypophysial and pineal tumors and are difficult to diagnose, although ventriculography may help.

Ataxia is a frequent and important symptom of tumor of the brain in childhood and may occur in cases of supratentorial or subtentorial growths. It may be cerebellovestibular, due either to hydrocephalus, with pressure on the cerebellum, or to choked labyrinth, but clinically there also occur frontal and temporal ataxias. Frontal ataxia is less severe; the deviation is contralateral, and vestibular signs are present only occasionally. Temporal ataxia resembles the frontal variety, but with more severe vestibular involvement, possibly because the temporal lobe is the cortical center for vestibular function.

Convulsions are common with the tumors of childhood and are more undifferentiated than those seen in adults. Their frequency depends on the accompanying hydrocephalus and to a lesser degree, on the site and nature of the tumor, blood vessel growths being particularly likely to cause epilepsy.

As to the type of tumors occurring in childhood, the views of Cushing and his group are accepted. The relative frequency of tumors of the glioma group is due to the immaturity of the cell types of which these tumors are composed and their consequent faster development and earlier appearance. The malignant nature of these neoplasms invalidates neurosurgical skill, except for the astrocytomas and some cystic tumors.

CHODOFF, Washington, D. C. [ARCH. NEUROL. & PSYCHIAT.]

COMBINATION OF FRIEDREICH'S ATAXIA AND CHARCOT-MARIE-TOOTH ATROPHY IN EACH OF TWO BROTHERS. ALEXANDER T. ROSS, J. Nerv. & Ment. Dis. **95**:680 (June) 1942.

Ross points out the rather close relationship existing in certain cases between Friedreich's ataxia and peroneal muscular atrophy of the Charcot-Marie-Tooth type. Cases partaking of the characteristics of both these syndromes have been described by many investigators. Ross

reports the cases of 2 brothers presenting a combination of these two conditions. A sister has undoubted Friedreich's ataxia, and a maternal cousin is a high grade moron with signs of mild involvement of the pyramidal tract and "Friedreich feet." One of the brothers reported is a moron with slurred speech, bilateral weakness of the external rectus muscles, nystagmus, bilateral cerebellar signs, weakness and pronounced atrophy of the peripheral musculature of the extremities, absence of deep reflexes and diminution to loss of all modalities of sensation in a glove and stocking distribution. Examination of the other brother gave similar results, with a more pronounced degree of mental defect.

The observations on this family lend support to the belief that the neurologic heredodegenerative diseases represent an abiotrophy of certain parts of the nervous system, which in individual cases may manifest itself in isolated abortive or bizarre combinations. The relation of these cases to the syndrome of Roussy and Lévy and to the familial spastic paraplegias is discussed. CHODOFF, Langley Field, Va. [ARCH. NEUROL. & PSYCHIAT.]

PNEUMOCOCCAL MENINGITIS. HARRY F. DOWLING, CARL C. DAUER, HARRY A. FELDMAN and CLARENCE R. HARTMAN, New England J. Med. **226**:1015 (June 25) 1942.

An analysis of all the cases of pneumococcic meningitis, 72 in number, occurring in the District of Columbia between Jan. 1, 1938 and Oct. 31, 1941 is presented.

Only 4 of the patients survived (5.5 per cent), all of whom were classified among the group of 39 patients who received good treatment with sulfonamide drugs or specific serum or both. Fifty-one cases, or 71 per cent of the whole series, occurred during the late fall and winter months, November to March, inclusive. The largest percentage of patients were children under 1 year of age (31 per cent) and the next largest adults over the age of 60 years (15 per cent).

A history of infection of the middle ear and pneumonia during or immediately preceding the development of meningitis was found in a large proportion (58 per cent) of the cases.

GENGENBACH, Denver.

RELATION OF CEREBRAL DYSRHYTHMIA TO ECLAMPSIA. GEORGE L. MALTBY and MILTON ROSENBAUM, Proc. Soc. Exper. Biol. & Med. **50**:10 (May) 1942.

Electroencephalographic tracings were taken from 17 patients for whom a diagnosis of eclampsia was made because of convulsive seizures associated with the latter part of the puerperium, the studies being made from one week to five years after their hospital admission. Thirteen of the 17 tracings were abnormal, 2 were borderline and the other 2 were considered to be within normal limits. In contrast, 16 tracings made on patients who had had toxemia of pregnancy without convulsions showed only 1 record to be abnormal and 2 borderline. For 10 of 17 patients with eclampsia there was a history of convulsive seizures in the patient or the immediate family. In the group with toxemia alone only 1 had a family history of convulsions. It appears that there may be a primary cerebral dysrhythmia in patients with eclampsia, and the toxemia serves as the "trigger mechanism" to cause convulsions. These studies are to be extended to note an effect of diphenylhydantoin sodium and other anticonvulsants in the eclamptic and preeclamptic states.

HANSEN, Minneapolis.

CALCIFIED EPENDYMOBLASTOMA OF THE FOURTH VENTRICLE IN A FOUR-YEAR-OLD GIRL: ROENTGEN DEMONSTRATION. EDWIN BOLDREY and EARL R. MILLER, Radiology **38**:495 (April) 1942.

A white girl 3 years and 7 months of age was well until two and a half months before coming to the hospital. She had had periodic nausea, vomiting and anorexia. Spasticity, ataxia, cracked pot percussion note and papilledema were present later. Roentgenograms showed a calcified midline lesion in the posterior fossa. The child was given 1,900 r through each of two ports, and temporary improvement followed. Approximately nine months later a craniotomy revealed a firm grayish red growth which extended from the aqueduct of Sylvius through the fourth ventricle and foramen of Magendie to the level of the lamina of the second cervical vertebra. Its only attachment was in the midline near the calamus scriptorius. It was necessary to clip a large vessel in detaching the tumor. Retrograde thrombosis led to extensive medullary necrosis and death on the second day.

This case is presented because of the rarity of calcification in the gliomas in children under 4 years of age. Rarer still is the demonstration by roentgenography of calcium in this type of tumor, especially when located in the posterior fossa. ANSPACH, Chicago.

THE PRESENT STATUS OF OPERATIVE TREATMENT FOR HYDROCEPHALUS. A. D'ERRICO, South. M. J. **35**:247 (March) 1942.

The author states that in many cases hydrocephalus is not amenable to surgical treatment and that it is important to recognize these cases. In some, only palliative relief can be given, but operation is certainly justifiable to prevent the disability which occurs with prolonged increase of pressure. An appreciable hydrocephalus may be present long before abnormal enlargement of the head is apparent.

Early study and recognition are essential, and as soon as a progressive dilatation is established operation should be done at once.

Any surgical measures for patients who already have an extreme hydrocephalus or a disability preventing a useful existence is not justified. The purpose of operation is to prevent the formation of an excessive hydrocephalus rather than to arrest it once it has formed.

SCHLUTZ, Chicago.

INTRACRANIAL TUMORS IN CHILDREN. W. A. SMITH and E. F. FINCHER, South. M. J. **35**:547 (June) 1942.

The authors made a preliminary review of 100 intracranial tumors in childhood. Eighty-six per cent of 87 verified growths were gliomas, and 63 per cent were studied below the tentorium.

Of 60 gliomas classified histologically, 50 per cent were medulloblastomas, 36 per cent astrocytomas and 10 per cent ependymomas. These constitute the predominant types of intracranial tumors in children.

SCHLUTZ Chicago.

SPINAL EXTRADURAL CYSTS. FRANK H. MAYFIELD and EVERETT G. GRANTHAM, Surgery **11**:589, 1942.

Mayfield and Grantham add 2 cases of extradural spinal cyst to the 14 already reported in the literature. They suggest that the condition may be more common than the small number of reported cases indicates. The symptoms may resemble those of multiple sclerosis closely, and hence in some cases operation may never be performed.

The cyst in 1 of the cases communicated through its pedicle with the subarachnoid space. It was emptied and filled several times at operation before it was removed in order to demonstrate the communication clearly. The authors suggest that such intermittent changes in volume may account for the remission of symptoms often observed in cases of this lesion. Their case supports the hypothesis that extradural cysts arise from herniations of the arachnoid through defects in the dura. The symptoms followed an injury initially, and the authors point out that the dural defect may be traumatic in origin. The second case was notable because of a history of four remissions of symptoms.

In most of the cases described symptoms developed in adolescence. Paraplegia appearing at this time of life should be followed by careful search for evidences of tumor of the spinal cord even though sensory disturbances and pain may be minimal or absent.

DRAYER, Philadelphia. [ARCH. NEUROL. & PSYCHIAT.]

CONTRAST MEDIA IN CYSTS AND ABSCESSES OF THE CEREBRAL HEMISPHERE. EDGAR A. KAHN, Surg., Gynec. & Obst. **74**:983 (May) 1942.

Air and iodized poppyseed oil have been used as contrast mediums in identification of cerebral cysts and abscesses, but each has its disadvantages. A colloidal suspension of thorium dioxide has advantages over both of them. Its use in 3 reported cases of tumor allowed the surgeon to make small localized openings and thus decreased the hazards of operation. Further localization and drainage in 3 other cases of cerebral abscess were greatly aided by injection of colloidal thorium dioxide in the original abscess cavity in which secondary drainage was necessary.

GOTTEN, Memphis, Tenn. [ARCH. NEUROL. & PSYCHIAT.]

PNEUMOCOCCAL MENINGITIS IN AN INFANT. A. SAKULA, Lancet **1**:444 (April 11) 1942.

Primary pneumococcic meningitis in a 17 month old boy was successfully treated with 74 Gm. of sulfapyridine.

In treating pneumococcic meningitis, particularly in infants, large doses of sulfapyridine are essential. A high initial dosage should be given, and the drug should be continued for at least a week after the temperature has subsided and the cerebrospinal fluid has become sterile.

LANGMANN, New York.

DISCUSSION ON INTRACRANIAL INJURIES IN CHILDHOOD. W. C. NORTHFIELD and W. G. WYLLIE, Proc. Roy. Soc. Med. **35**:393 (March) 1942.

Dr. W. C. Northfield states that his experience with intracranial injury in children has been for the most part acquired since the onset of the war. He reports on 43 cases, the patients ranging in age from 3 months to 14 years. In 35 cases the injury was closed, and in 11 of these it was sustained in an air raid. Analysis of these 35 cases then follows. Eight cases involved open injuries, and these are also analyzed. The follow-up of the children was not as thorough as desired, and at the time of the report of 15 patients with closed injury 4 still suffered from occasional slight headache; the others were all quite normal. One of 3 children with an open injury still suffered from headache. Epilepsy occurred in 3 cases. From his review he found that the incidence of fissure fractures of the vault in closed injuries is much higher in children than in adults and often there is no loss of consciousness, probably owing to the greater fragility of the child's skull, which, although possibly more elastic, is yet much thinner than that of an adult. On the other hand, a child tolerates a cerebral injury much better than an adult and recovers from it much more rapidly and completely.

Dr. W. G. Wyllie believes that similar problems occur with intracranial injuries of children and with those of adults, yet he feels there are some differences both in the immediate effects and in the after-effects of such injuries. These he illustrates in the paper by case histories. The most frequent clinical features of head injuries that he mentions in detail are:

1. Concussion.

2. Vascular and other lesions. When unconsciousness is prolonged or a lucid interval is followed by unconsciousness or irritation or stupor, the possible causes difficult to differentiate include (*a*) subarachnoid hemorrhage, (*b*) contusion, (*c*) cerebral edema, (*d*) subdural and extradural hemorrhage and (*e*) sepsis.

3. Pupillary changes. Lumbar puncture, ventriculography and operative exploration may have to be performed for diagnostic purposes. The child as a rule escapes the late effects of an intracranial injury more than the adult.

WILLIAMSON, New Orleans.

HEREDODEGENERATIVE CEREBELLAR DISORDERS. ANTONIO R. DE MELLO, Arch. brasil. de med. **32**:109 (April) 1942.

After a brief history of the development of the present concept of the hereditary cerebellar disorders, Mello describes a case which he had the opportunity of studying clinically and pathologically. The observation concerns a woman whose disease began at about 29 years of age with unsteadiness of gait, which steadily progressed. Examination two months before death, at the age of 36, disclosed fixed facies, apathy, exophthalmos, slight ptosis, inability to walk, general muscular weakness and atrophy, especially in the distal parts of the lower extremities, slight asynergy on voluntary movement of the arms, a bilateral Babinski sign, exaggerated patellar reflexes and incontinence of feces and urine. The patient could scarcely speak even a few syllables and had great difficulty in swallowing. She died of pneumonia. Several members of the family, representing at least three generations, had a similar complaint. Anatomic study revealed atrophy of the cerebellar cortex and sclerosis of the cerebellar tracts, the pyramidal tracts and the fasciculi of Goll.

The author offers this case in support of Austregesilo's thesis of the close relationship of Marie's cerebellar ataxia, Friedreich's ataxia and peroneal atrophy. He proposes to call the condition in his case spinocerebellar heredoataxia.

BAILEY, Chicago. [ARCH. NEUROL. & PSYCHIAT.]

EPIDURAL ABSCESS WITH PURULENT MENINGITIS. ROBERTO MACHEDO, F. BORGES Y HERNANDEZ and E. FERNANDEZ DEL MORAL, Arch. de med. inf. **11**:77 (April-June) 1942.

Machedo and co-workers report a case of epidural abscess with purulent meningitis apparently secondary to an abscess in the neck. Autopsy showed a large extradural abscess due to staphylococci.

SANFORD, Chicago.

Psychology and Psychiatry

FAMILIAL MENTAL DEFICIENCY AKIN TO AMAUROTIC IDIOCY AND GARGOYLISM: AN APPARENTLY NEW TYPE. GEORGE A. JERVIS, Arch. Neurol. & Psychiat. **47**:943 (June) 1942.

A new type of familial mental deficiency is reported in 6 members of one family. All of them had severe idiocy, stunted growth due to shortness of the legs, peculiar facies and changes in the bones of the skull, consisting of abnormal thickness of the calvarian bones, widely separated tables and a peculiar spongy appearance of the osseous tissues of the diploe. Patho-

logically, there was swelling of the nerve cells with cytoplasmic infiltration of lipid granules. There was consanguinity in the family. The condition is probably inherited as a recessive trait.

BEVERLY, Chicago.

ELECTROENCEPHALOGRAPHIC STUDIES IN CHILDREN PRESENTING BEHAVIOR DISORDERS. LAZARUS SECUNDA and KNOX H. FINLEY, New England J. Med. **226**:850 (May 21) 1942.

Jasper, Solomon and Bradley, in their studies of childhood behavior disorders, noted that 71 per cent of the patients had abnormal electroencephalograms. Half of the abnormal tracings were found in cases in which there was no other objective evidence of cerebral dysfunction. In the present study Secunda and Finley found:

Of 143 children presenting behavior disorders, 26 per cent had normal, 23 per cent borderline and 51 per cent abnormal electroencephalograms, whereas of the 76 controls, 68 per cent had normal, 17 per cent borderline and 15 per cent abnormal tracings. As a group, the electroencephalograms of the children presenting behavior disorders were more vulnerable to hyperventilation than those of the controls. Twenty-four (16 per cent) of the children with behavior disorders had inferior intelligence; of these, 15 (62 per cent) had abnormal tracings. Of the 119 who had normal intelligence, 59 (50 per cent) had abnormal tracings. This is not a significant difference.

The patients and controls were divided into age groups: 4 to 9, 10 to 12, 13 to 15 and 16 to 18 years. The records of the behavior disorders, age group compared with age group, showed a progressive increase in normal records and a diminution in immature-abnormal records with increase in age (from 74 per cent in the group from 4 to 9 years to 34 per cent in that from 16 to 18). The possibility that the decrease in immature-abnormal records in the older age group was related to the maturation of the cerebrum is discussed.

GENGENBACH, Denver.

Diseases of the Genitourinary Tract

CHEMOTHERAPY WITH THE SULFONAMIDE COMPOUNDS. HENRY F. HELMHOLZ, Wisconsin M. J. **41**:472 (June) 1942.

Emphasis is placed on the fact that only small doses of the sulfonamide compounds are needed to clear up most urinary infections.

For infections due to Escherichia coli, Aerobacter aerogenes, Proteus ammoniae, Pseudomonas aeruginosa, Staphylococcus albus and Salmonella, sulfathiazole is definitely superior to sulfanilamide. Two to 4 Gm. per day is the average dose for urinary infections. A concentration of 50 mg. per hundred cubic centimeters of urine can be relied on for each gram given per day when the renal function is normal. The same concentration is also more effective in an acid urine, an important fact to make use of in cases of resistant infections.

Streptococcus faecalis is highly resistant to the sulfonamide compounds, but by acidifying the urine to a p_H of 6 or 5.5 it is usually destroyed. If not, mandelic acid should be used.

JANNEY, Wauwatosa, Wis.

THE SECRETION OF URINE BY DEHYDRATED AND NORMAL INFANTS. W. F. YOUNG and R. A. MCCANCE, Arch. Dis. Childhood **17**:65 (June) 1942.

Infants aged 1 to 8 months have been found to have kidneys which are intermediate in functional capacity between those of adults and those of newborn children.

They have lower glomerular filtration rates and lower urea clearances than adults, expressed on the basis of surface area, and both vary with the minute volumes at normal rates of flow of urine. The mineral clearances also tend to be lower than in later life. The concentrations of solids in the urine do not rise as in adults when the minute volumes fall. Consequently, infants fail to maintain a constant internal milieu the moment they begin to pass small volumes of urine.

No evidence has been obtained that children who have been made short of water by diarrhea or vomiting have a specific renal lesion. Their kidneys are functioning in the normal infantile manner, and the abnormalities in their serum chemistry are due to the small amount of water available for excretion.

KELLY, Milwaukee.

THE CONCENTRATION OF RENIN IN THE BLOOD OF DOGS RENDERED HYPERTENSIVE BY RENAL ISCHEMIA. E. DELL'ORO and E. BRAUN-MENENDEZ, Rev. Soc. argent. de biol. **18**:65 (May) 1942.

In dogs whose right kidney had been extirpated, the left kidney was explanted under the skin of the lumbar region. The renal artery was then constricted by a Goldblatt clamp. The

amount of renin in the blood obtained by puncture of the renal vein through the integument and in the blood of the femoral artery before and after constriction of the renal artery was estimated.

Renin was not found in 12 cc. of plasma drawn from the renal vein or from the femoral artery before constriction of the renal artery. After constriction of the artery and coincident with the rise in blood pressure, 0.05 to 0.8 and 0.22 to 1 unit of renin were found in 12 cc. of plasma from femoral blood and renal venous blood respectively.

McCUNE, New York.

Diseases of the Ductless Glands; Endocrinology

1. HORMONES OF THE ADRENAL CORTEX. EDWARD C. KENDALL, Endocrinology **30**:853 (June) 1942. 2. FUNCTIONS OF THE ADRENAL CORTEX. FRANK A. HARTMAN, ibid. **30**:861 (June) 1942. 3. A DISCUSSION OF THE MECHANISM OF ACTION OF ADRENAL CORTICAL HORMONES ON CARBOHYDRATE AND PROTEIN METABOLISM. C. N. H. LONG, ibid. **30**:870 (June) 1942.

These three papers appearing in the twenty-fifth anniversary number of the *Journal of Endocrinology* together form an excellent review of the knowledge of the adrenal cortex and its functions.

JACOBSEN, Buffalo.

ADVANCEMENT OF KNOWLEDGE OF THE ROLE OF THE HYPOPHYSIS IN CARBOHYDRATE METABOLISM DURING THE LAST TWENTY-FIVE YEARS. B. A. HOUSSAY, Endocrinology **30**:884 (June) 1942.

Houssay presents a condensed review of the important known facts.

JACOBSEN, Buffalo.

RESPONSE OF THE VAGO-INSULIN SYSTEM TO ANOXIA AS DEMONSTRATED IN ADRENALECTOMIZED DOGS. IRVINE McQUARRIE, M. R. ZIEGLER and L. J. HAY, Endocrinology **30**:898 (June) 1942.

The effects of anoxia (breathing 5 per cent oxygen plus 95 per cent nitrogen) on the blood sugar level and on the plasma potassium and inorganic phosphate levels of normal, adrenalectomized and adrenalectomized-pancreatectomized dogs were determined. Whereas normal dogs showed a rise, adrenalectomized animals showed a fall in blood sugar. The results of the experiments are interpreted as evidence that the vagoinsulin, as well as the sympathoadrenal, system is excited by asphyxia.

JACOBSEN, Buffalo.

PREVENTION OF EXPERIMENTAL GASTROJEJUNAL ULCER BY ENTEROGASTRONE THERAPY. A. P. HANDS, H. GREENGARD, F. W. PRESTON, G. B. FAULEY and A. C. IVY, Endocrinology **30**:905 (June) 1942.

It has been clearly established that the parenteral administration of an extract of the upper intestinal mucosa, containing a chalone called enterogastrone, depresses the motor and secretory activity of the stomach. It is shown that treatment with enterogastrone extract has a remarkable potency in preventing jejunal ulcer in dogs in which gastrojejunostomy has been performed in a manner which in untreated animals invariably produces ulcer.

JACOBSEN, Buffalo.

COMMERCIAL ENDOCRINE PREPARATIONS. ELMER L. SEVRINGHAUS, Endocrinology **30**:912 (June) 1942.

After a review of the present status of commercial endocrine preparations it is concluded that clinicians are justified in asking that improved methods be set up to assure uniform potency as well as stability and dependability as to type of action of endocrine materials. The obvious group in the United States to assume the task of bringing order out of the present confusion in the field of endocrine preparations is the Association for the Study of Internal Secretions.

JACOBSEN, Buffalo.

PSEUDO-HYPOPARATHYROIDISM—AN EXAMPLE OF SEABRIGHT-BANTAM SYNDROME. FULLER ALBRIGHT, CHARLES H. BURNETT, PATRICIA H. SMITH and WILLIAM PARSON, Endocrinology **30**:922 (June) 1942.

Theoretically one should obtain essentially the same clinical picture from failure of an end organ to respond to a hormone as from a decreased production or absence of the hormone. Three cases are here presented in which the clinical findings were those of idiopathic hypoparathyroidism but in which evidence was obtained to suggest strongly that the disturbance was not a lack of the hormone but a resistance to it.

The evidence that the patients were resistant to parathyroid hormone was as follows: (*a*) The abnormal serum calcium and phosphorus values for all 3 patients failed to deviate toward normal with the administration of parathyroid extract in large amounts; (*b*) 2 patients (cases 1 and 2) failed to show a phosphate diuresis following intravenous administration of parathyroid extract; (*c*) 1 patient (case 1) was found to have normal parathyroid tissue on surgical exploration.

All 3 patients had a peculiar physiognomy characterized by a round face and a rather thick-set figure. The index fingers of 1 patient (case 1) were longer than the middle fingers.

JACOBSEN, Buffalo.

THE ESTROGENS. EDWARD A. DOISY, Endocrinology **30**:933 (June) 1942.

A review of the progress in the field of the estrogens over a period of twenty-five years is given.

JACOBSEN, Buffalo.

ESTROGENIC HORMONES IN THE GENESIS OF TUMORS AND CANCERS. EDGAR ALLEN, Endocrinology **30**:942 (June) 1942.

A review of the literature concerning the effects of estrogens on many varieties of tumor growths is given. It is concluded that endocrine secretions appear as important factors in the genesis of some atypical growths, including certain tumors and cancers.

JACOBSEN, Buffalo.

MAMMOGEN AND UNILATERAL MAMMARY GLAND GROWTH IN THE RABBIT. A. A. LEWIS and C. W. TURNER, Endocrinology **30**:985 (June) 1942.

Unilateral percutaneous treatment of male rabbits with estrone or diethylstilbestrol caused either greater development of the mammary glands on the treated side or in some cases development of treated glands only. Cutaneous irritants applied in a similar manner produced essentially negative results.

JACOBSEN, Buffalo.

THE CLINICAL ASPECTS OF DWARFING. E. KOST SHELTON, Endocrinology **30**:1000 (June) 1942.

The following classification of dwarfism and infantilism based on the etiologic factor is proposed:

1. Inherent or constitutional factors (as in so-called primordial dwarfism and in normal small-statured persons)
2. Congenital disturbances of the skeleton (as in achondroplasia, mongolism and micromelic dwarfism)
3. Anomalies of the circulatory and urinary systems (as in congenital cardiac and renal disease, angioplastic infantilism and renal rickets)
4. Disturbances of nutrition
   - A. Inadequate food, vitamin and mineral intake (as in slow starvation, rickets and other deficiency diseases)
   - B. Inadequate absorption of the building essentials from disturbance of the gastric, intestinal and pancreatic enzymes (as in hypochlorhydria, celiac disease, refractory rickets, infection with intestinal nematodes)
   - C. Inadequate utilization or deposition of the essential elements from various metabolic and endocrine disorders (as in hypothyroidism, hypopituitarism, diabetes)
5. Chronic infectious disorders (as in tuberculosis and syphilis)

Discussion of these types and their treatment is given, along with a number of case reports of children in whom growth had been accelerated by endocrine therapy. It is concluded that growth is an extremely complex phenomenon, especially in primates, and no secreting organ of the body may be entirely exempt from exerting an influence in its production.

JACOBSEN, Buffalo.

EFFECT OF CERTAIN HORMONES AND DRUGS ON THE PERFUSED MAMMARY GLAND. W. E. PETERSEN, Proc. Soc. Exper. Biol. & Med. **50**:298 (June) 1942.

The effect of a number of substances on the mechanism of blood flow and of milk ejection was studied by means of perfused bovine mammary glands. The substances were injected into the arterial blood as it entered the gland, and the teats were cannulated to permit drainage of the milk immediately. Pitocin and acetylcholine caused complete evacuation of

milk from the gland. Pitressin caused an incomplete evacuation and a decrease in blood flow. Epinephrine and histamine caused a decrease in blood flow with a decrease in the ejection of milk. Ergonovine caused some vasoconstriction, but had no effect on the ejection of milk. Acetylbeta methylcholine (mecholyl) caused but a partial evacuation of milk from the gland. Carbamylcholine (lentin) had no effect on milk ejection. Atropine tended to increase the blood flow and completely prevented any response to acetylcholine and acetylbetamethylcholine but had no effect on the action of pitocin or of pitressin. These experiments indicate that the mammary is innervated with the parasympathetics as well as the sympathetics.

HANSEN, Minneapolis.

Diseases of the Muscles, Bones, Joints and Lymph Glands

ROENTGEN SIGNS OF EARLY SUPPURATIVE ARTHRITIS OF THE HIP IN INFANCY. L. K. CHONT, Radiology **38**:708 (June) 1942.

Among the etiologic factors, infections of the upper respiratory tract, sometimes very mild, and insignificant-looking furuncles located either close to or distant from the involved hip are common. Many times only the most attentive questioning of the parents can recall these trivial lesions which may have occurred, and probably healed, days prior to the onset of symptoms in the hip. In other cases there is a preceding history of bronchopneumonia, osteomyelitis or meningitis.

Of 6 patients reported on by the author, 3 had infections of the respiratory system, 1 had bronchitis, 1 had lobar pneumonia and the third had bronchopneumonia prior to the onset of coxitis. In 2 other cases the lesions were secondary to pneumococcic meningitis and furuncle, respectively, while in the sixth case no history of a preceding illness or lesion was obtained.

Since the infection is blood borne, the general clinical symptoms are those of toxemia, increasing prostration, fever and leukocytosis. The local symptoms consist of pain, swelling, and impaired function of the hip followed by muscle spasm, loss of the gluteal fold and flexion of the thigh. In the author's cases the temperature varied between 101 and 105.8 F., with an average of 103.2 F. The red blood cell count varied from 1,000,000 to 3,890,000, averaging 2,791,667, and the white cell count was between 10,900 and 30,800, with an average of 17,316.

The pathologic process begins with an enhanced secretion of serum into the joint cavity, resulting in an increased intracapsular pressure. Because of the anatomic structure of the infantile hip joint, a lateral and upward subluxation or dislocation of the femoral head occurs. Later the increased synovial fluid becomes purulent and destroys the articular cartilage, which results in ankylosis or telescoping of the hip.

Roentgen examination not only is a safe diagnostic procedure but gives reliable information as to the extent of the disease and the approximate amount of intracapsular fluid. It will differentiate a true infectious arthritis from an allergic one due either to a systemic disease or to a localized lesion, since in the latter the roentgenogram shows normal conditions.

Because of the anatomic structure of the infantile hip joint and the greatly increased intracapsular fluid, a lateral and upward subluxation or dislocation of the femoral head occurs. The increased synovial fluid becomes purulent and destroys the articular cartilages, and a permanent crippling results if surgical intervention is delayed. Roentgen examination is a reliable diagnostic procedure, revealing also the extent of the disease and the amount of intracapsular fluid present. It will further differentiate a true infectious arthritis of the infantile hip.

ANSPACH, Chicago.

Diseases of the Eye

A CASE OF RETINOBLASTOMA. P. LA ROCHELLE, Union méd. du Canada **71**:577 (June) 1942.

A boy of 3½ years struck his left eye accidentally. The parents noticed that the eye was filled with blood. He was taken to an ophthalmologist, who ordered atropine sulfate drops instilled. Ten weeks later he was seen by the author, who immediately instilled miotics (pilocarpine hydrochloride and physostigmine salicylate). The eyegrounds could not be seen until seven months after the injury, at which time a yellowish mass could be made out. Enucleation was advised, and a retinoblastoma was removed a week later.

DAFFINEE, Melrose, Mass.

A STUDY OF THE HEMIANOPIAS. L. ROSEN, Confinia neurol. **4**:271, 1942.

Rosen has made an analysis of the frequency, cause and localization of the disease process in 97 cases of hemianopia. Injuries to the vascular system, namely, hemorrhage, thrombosis

and embolism, were among the most frequent causes of lesions situated central to the chiasm. Tumors constituted the next most frequent cause, and syphilis came third. On the other hand, tumors were far more numerous in cases of the heteronymous hemianopias localized at the optic chiasm. In the vascular group by far the larger proportion of the patients were affected after the age of 40. About half the patients with chiasmal lesions were between the ages of 40 and 60 years. DeJong, Ann Arbor, Mich. [Arch. Neurol. & Psychiat.]

Skin Diseases; Allergy

Influence of Acute Infection on the Plasma Lipids and the Course of Eczema. Albert V. Stoesser, J. Allergy **13**:248 (March) 1942.

A group of 9 infants with infantile eczema were kept under careful observation in a hospital. The cutaneous changes were watched and determinations of plasma lipids were made during an attack of acute disease that each infant had. There was a short period of improvement in the cutaneous condition at the onset of the disease, followed by an aggravation of the eczema. The height of the infection usually marked the peak of the flare-up in the condition of the skin, and this was the time when the degree of unsaturation of the serum fatty acids was lowest.

It is assumed that the acute respiratory diseases cause the eczema to become worse through the medium of depressing the serum unsaturated fatty acids to low levels and that improvement in the condition of the skin takes place during the convalescent period because there is a corresponding gradual return of the unsaturation of the fatty acids. Hoyer, Cincinnati.

Odors (Osmyls) as Allergenic Agents. Erich Urbach, J. Allergy **13**:387 (May) 1942.

Osmyls are odoriferous particles, which can act as allergens when inhaled. Hypersensitivity to the scent of trees, plants or flowers without an associated sensitivity to their pollens may explain the failure of treatment when extracts of the pollens are used. When the odoriferous particles (for preparation of a desensitizing material) cannot be extracted from the flower, the process of enfleurage is used. In this way the particles are taken up by lard, which acquires the taste and smell of the flower. Desensitization is accomplished by the oral administration of the lard. Hoyer, Cincinnati.

Treatment of Asthmatic Paroxysm with Nicotinic Acid: Preliminary Report. Fred E. Maisel and Eugene Somkin, J. Allergy **13**:397 (May) 1942.

Nicotinic acid in doses of 0.1 Gm. was given intravenously to a small group of patients with asthma that had failed to respond to the usual treatment. Relief was obtained within three to five minutes by 75 per cent of the patients and lasted three to fifteen hours. Freedom from attacks or a lessening of the severity was obtained by continued use of 0.2 Gm. of nicotinic acid orally four times a day.

It is felt that nicotinic acid may be an adjunct to other therapeutic agents.

Hoyer, Cincinnati.

Milk Sensitization. George E. Rockwell, J. Allergy **13**:404 (May) 1942.

The author calls attention to the fact that certain antigens eaten by a cow may pass intact into the milk. A person supposedly sensitive to milk may in reality be sensitive to an antigen that the cow has eaten. The case is reported of a young farmer who was sensitive to alfalfa. Asthma developed whenever the patient came into contact with it or when he drank milk obtained from cows which had been fed alfalfa.

He was treated successfully for his asthma and eczema by the administration of small doses of alfalfa extract for a period of six months, during which time he avoided all other contact with alfalfa. Hoyer, Cincinnati.

Mecholyl Desensitization in the Treatment of Asthma. R. Bruce Logue and Clarence Laws, J. Allergy **13**:414 (May) 1942.

Mecholyl chloride was used in small doses hypodermically in treating 24 patients with chronic asthma. It was thought that it might increase the production of cholinesterase and thus destroy acetylcholine, which may be the cause of the spasm.

The results obtained led the author to feel that mecholyl chloride has no value in the hyposensitization treatment of asthma. Hoyer, Cincinnati.

PILI TORTI HEREDITARIA [SIC]. BERNARD APPEL and SALVATORE J. MESSINA, New England J. Med. **226**:912 (June 4) 1942.

The name "pili torti" was first applied by Ronchese in 1932 to a rare developmental anomaly of the hair. He reported the case of a 7 year old girl. The teeth were poor and slightly notched, with spaces between them; the hairs on the scalp were dull blond, lank and frizzly, with a wild bushy appearance. The hair was characterized by fragility and sharp twists on its own axis.

The sister, two years younger, showed a similar but much milder condition. There was a moderate degree of alopecia of the outer two thirds of the eyebrows. This patient did not show any dental hypoplasia.

In the case reported by the authors as one of "pili torti hereditaria" (the last word should be "hereditarii"), the mother stated that the patient had had a peculiar twisting type of hair since birth. Bald areas over the scalp and over the eyebrows were present constantly and were very disturbing. An older brother and a younger sister of the patient had a similar but definitely less noticeable type of hair. A paternal aunt and a grandmother were similarly affected. This was as far back as any cases of the condition were known to the parents.

The cause of this condition is not definitely known. It is obviously a developmental anomaly, and it may well belong to the general classification of ectodermal dysplasia. As the patients become older, there is a natural tendency for the hair to become less abnormal in appearance. The application of hydrous wool fat is apparently the only effective treatment known at present.

GENGENBACH, Denver.

SULFATHIAZOLE OINTMENT IN THE TREATMENT OF PYOGENIC DERMATOSES. EARL A. GLICKLICH, New England J. Med. **226**:981 (June 18) 1942.

The author reports on 42 patients with eight different dermatologic diseases which were caused by pyogenic organisms (mostly hemolytic Staphylococcus aureus). The strength of the sulfathiazole, 5, 10 or 15 per cent, made little difference; the infections cleared more quickly, as a rule, than infections treated by other means; toxic effects were not observed, and the application of sulfathiazole to the skin for forty-eight hours caused only insignificant amounts of the drug in the blood stream.

GENGENBACH, Denver.

PENETRATION OF SULFONAMIDES THROUGH INTACT SKIN BY IONTOPHORESIS AND OTHER MEANS OF LOCAL APPLICATION. WILLIAM G. CLARK, ERNEST A. STRAKOSCH and CLARICE NORDLUM, Proc. Soc. Exper. Biol. & Med. **50**:43 (May) 1942.

The authors studied the penetration of sulfathiazole into the skin of rats, rabbits and human subjects from wet dressings, by iontophoresis and from an ointment base. The penetration of sodium sulfathiazole from prolonged application of wet dressings was greater than that by iontophoresis, but the effect was essentially the same when the dressings were applied up to six hours. The effect obtained from an ointment base was definitely less than that by the other two methods. The effect of impaired circulation was also studied.

HANSEN, Minneapolis.

TREATMENT OF HEMANGIOMATA, WITH SPECIAL REFERENCE TO UNSATISFACTORY RESULTS. WILBUR BAILEY and WILLIAM S. KISKADDEN, Radiology **38**:552 (May) 1942.

Most disfiguring lesions and other forms of unsatisfactory results are attributed to the selection of a therapeutic agent without regard to its fitness for the particular type or shape of hemangioma which is to be treated.

Approximately one third of all infants show birthmarks in the first year of life. One half of these involve the head and neck. The incidence in females is twice that in males.

There are three types of vascular birthmarks from a clinical and pathologic standpoint, but all may be present in the same tumor.

1. Capillary hemangioma, or "port wine stain" (hemangioma simplex), consists of an increased number of venules and capillaries beneath a thin velvety epidermis. Irregular patches of redness are usually in the eyelids, nose, forehead or nuchal region in the newborn. These invariably disappear six or eight months after birth. This disappearance rarely occurs in other forms of hemangioma. The vessels of these capillary hemangiomas have a well differentiated lining of the adult variety and explain the resistance to radium and roentgen rays. Ultraviolet treatment with an air-cooled quartz mercury vapor arc lamp, thought by MacCollum to help in certain instances in which blanching occurs on pressure, gives good results in twelve weeks or the treatment has failed. Treatment consists of excision, use of ultraviolet rays and application of cosmetic pastes in selected cases.

2. Strawberry mark hemangioma involves the true skin and submucosa, "hypertrophic endothelial hemangioma" (Young). Masses of endothelial cells are found displacing the skin and subcutaneous tissues. The surface is irregular and red. Vessels may collapse because of rapid growth of the tumor.

3. Cavernous hemangiomas are deep lying tumors, sometimes seen as a purplish swelling through normal skin. They are located in subcutaneous tissues, mucosa, muscle and viscera. Typically these are large blood spaces lined by endothelium and separated by large connective tissue septums. The latter may remain after treatment and require surgical removal. However this is rare in the authors' experience.

Treatment of all types may require surgical intervention, but frequently excision is not practicable. There have been unsatisfactory results with types 2 and 3 from delay (rapid growth occurring) and from the selection of the wrong therapeutic agent. Solid carbon dioxide and radium are not suitable and are even dangerous for deep hemangiomas. Use of surgical measures for all these growths is too radical. Radon seeds should first be employed if the lesion is elevated. Radiation is recommended for the cavernous type, with a surgical procedure employed for removal of the residual mass of fibrous tissue. Electrocoagulation for cavernous types in adults that do not respond to radiation may be satisfactory, but sloughs are likely to produce unsatisfactory results. The use of sclerosing solutions was disappointing in the hands of the authors but is recommended for cavernous hemangiomas in adults if surgical excision is not possible. Small superficial lesions may be eradicated by use of solid carbon dioxide, but it should not be used for deep hemangiomas.

Radiation therapy in the form of radium is most useful for the hypertrophic endothelial or cavernous type if properly applied. It should be used early, as sensitivity of the tumor varies inversely as the age of the patient. Superficial tissue (skin) must be preserved. Roentgen therapy should be tried for very large lesions, but the end results were not as favorable in the experience of the authors as those from radium, even when the dosage was large enough to endanger the normal growth of surrounding epiphyses, bones and soft tissues. It is dangerous to use unfiltered radium against any but the most superficial lesions. Usually good results are obtained with proper filters using one or two doses of 700 to 1,000 gamma roentgens without damage to the skin. The authors favor distances of 3 mm. for superficial lesions and 1 to 3 cm. for deeper lesions. The radium must be arranged in a geometric design so that all portions of the tumor are irradiated as evenly as possible. To the filter of 0.5 mm. of platinum are added 1 mm. of silver and 0.5 mm. of brass as secondary filters. The skin following treatment of this kind returned entirely to normal. For the unusually deep lesions, gold radon seeds with a wall thickness of 0.2 mm. and a strength of 0.25 to 0.5 millicuries were planted in an appropriate geometric arrangement, so that one seed was in each cubic centimeter of tumor tissue. The distribution was such that the skin received less radiation than the tumor. Usually only one visit was necessary for the patient, and extremely satisfactory results were obtained.

ANSPACH, Chicago.

A CASE OF HOLOGYNIC INHERITANCE OF ICHTHYOSIS VULGARIS. TWISTON DAVIES and DONALD MCGREGOR, Brit. J. Dermat. **54**:121 (April) 1942.

A pedigree is reported in which ichthyosis vulgaris partially associated with eczema was inherited in a hologynic manner; i. e., all the females, and only the females, of the family were affected.

BLUEFARB, Chicago. [ARCH. DERMAT. & SYPH.]

Surgery and Orthopedics

SUBLUXATION OF THE HEAD OF THE RADIUS: A PEDIATRIC CONDITION. S. A. ANDERSON JR., South. M. J. **35**:286 (March) 1942.

The author describes subluxation of the head of the radius. Its incidence is about 1 per cent in children under 9 years of age admitted to the hospital for surgical treatment. Most of the patients are under 3 years of age. The exciting cause is sudden traction of the extended arm. The symptoms and signs are: loss of use, absence of deformity, tenderness over the head of the radius, limitation of complete flexion and extension by pain and especially limitation of complete supination by an obstruction and exquisite pain.

Reduction is accomplished by forced supination with the forearm flexed at 90 degrees or more. At the moment of reduction there is felt a click at the elbow, and thereafter all movements are free and painless.

SCHLUTZ, Chicago.

Teeth and Dentistry

DATA ON ERUPTION AND CARIES OF THE DECIDUOUS TEETH. CARL R. DOERING and MARGARET F. ALLEN, Child Development **13**:113 (June) 1942.

"From the case histories of children studied at the Center for Research in Child Health and Development, School of Public Health, Harvard University, data on the eruption of, and the development of caries in the deciduous teeth are presented in relation to age and sex of child, the jaws and the type of tooth.

"In general the order of eruption is as follows: the central incisors, the lateral incisors, the first molars, the cuspids and the second molars. About 12 per cent of children fail to conform to this pattern. There is evidence of early and late erupting groups of children. The period during which total dentition takes place varies from less than 12 months to over 33 months. Siblings tend to be similar in the average age of eruption. An age index of eruption is developed.

"Caries begin to appear at 3 years of age and increase almost uniformly each year. At 8½ years of age about 3 per cent of children have had no carious teeth. The second molar is the most vulnerable. Siblings tend to be similar in carious condition. An index of caries is presented."

[AUTHORS' SUMMARY]

Miscellaneous

INFLUENCE OF DIET ON SULFANILAMIDE TOXICITY. ISRAEL KAPNICK, CHAMP LYONS and JOHN D. STEWART, J. Pharmacol. & Exper. Therap. **74**:284 (March) 1942.

On a high protein (casein) diet young healthy albino rats tolerated large doses of sulfanilamide well, in contrast to rats on the general maintenance, high fat and high carbohydrate diets. As the authors suggest, this result may be due to the much lower content of sulfanilamide in the blood and the more rapid excretion of the drug by the animals fed the high protein diet.

PILCHER, Cleveland.

INTRAVENOUS AND SUBCUTANEOUS ADMINISTRATION OF ALKALI-TREATED BOVINE SERUM ALBUMIN TO MAN AND LOWER ANIMALS. HARRY A. DAVIS and A. G. EATON, Proc. Soc. Exper. Biol. & Med. **50**:246 (June) 1942.

Bovine serum albumin after being treated with sodium hydroxide was injected intravenously into guinea pigs, rabbits, white mice and dogs and then into human beings. Dogs were bled so that one third to one half of the blood volume was removed and the alkali-treated bovine serum albumin, injected intravenously, was able to maintain normal blood pressure with no untoward reactions. Cutaneous tests with 0.5 cc. of the albumin solution were given to 67 male and female subjects, and in none did reactions occur. Three men were given 50 cc. of solution by vein at the rate of 5 cc. per minute, and in 2 an increase in blood pressure of 6 to 14 mm. of mercury occurred, while in the third no change in blood pressure was noted. The authors believe that this alkali-treated bovine serum may be used as a substitute for blood in human subjects.

HANSEN, Minneapolis.

SULPHAMETHAZINE: CLINICAL TRIAL OF A NEW SULPHONAMIDE. D. W. MACARTNEY, G. STEWART SMITH, R. W. LUXTON, W. A. RAMSAY and J. GOLDMAN, Lancet **1**:639 (May 30) 1942.

Clinical trial is reported of sulfamethazine (2-[4'-aminobenzenesulfonylamido] 4, 6 dimethylpyrimidine) in 73 cases of lobar pneumonia and a few cases of meningococcic meningitis and gonorrhea. The preliminary results suggest that the preparation has high therapeutic efficiency and on account of its high solubility is unlikely to cause renal damage. The incidence of nausea and vomiting is much less than with sulfapyridine, and cyanosis is absent.

LANGMANN, New York.

Book Reviews

Your Child: His Family and Friends. By Frances Bruce Strain. Price, $2.00. Pp. 210, with 12 illustrations. New York: D. Appleton-Century Company, 1943.

The author of this book is a veteran contributor to *Parents Magazine,* and much of her material has appeared in that publication previous to this time. She, therefore, knows fairly well what the puzzled or inexperienced mother must be taught.

In this book Mrs. Strain has written about a wide variety of problems regarding the child and his environment. She covers the child's home, school, playground and other environmental factors.

While she offers nothing new on the subjects, her text is fairly good for the layman's need, as far as it goes. Unfortunately, the author is rather preciously freudian. In the reviewer's opinion, a child need not necessarily have a warped attitude toward marriage even if that child's parents do not have the "psychiatric approach" to problems.

Mrs. Strain's chapter on "Grandparents, Servants, and Guests" is good. Her statement that "whatever we, the parents, feel toward 'others' who form a part of the family, the children should be left free to make their own choices" and that "a person may not make a very satisfactory 'in-law'—unfortunately tradition is against them—but he may make a most satisfactory grandparent, uncle, or aunt" are evidence that under the "Freudian approach" there is a common sense person writing the book.

"Playground Problems" is another especially worth while chapter. The author strongly advises mothers who are overly protective (and are there any others?) to allow the normal development of their children to proceed, even if in that development they hear some undesirable words or see wrong acts. She says: "But—and this is a comfort—exposure does not necessarily mean infection and later complications. A wholesomely reared child builds up a certain immunity against undesirable experiences, does not catch the harm even if he is exposed to it."

Unfortunately, Mrs. Strain fails to feel that adolescence belongs to childhood and so omits that phase entirely from her book. If it were not for this omission, this book would have the reviewer's firm approval.

Care and Feeding of Children. By L. Emmett Holt Jr., M.D. Sixteenth edition. Price, $2.00. Pp. 321, with no illustrations. New York: D. Appleton-Century Company, 1943.

Dr. L. Emmett Holt Jr. has revised the book his father first wrote fifty years ago and has added new material. Since its first copyright, in 1894, the original book or its revisions have been read by many thousands of parents.

The newest edition offers solutions to a great many more problems than were discussed in previous editions. Some of the new sections are concerned with allergy, behavior problems, vitamins and inoculations.

In this volume the author almost too completely covers all the phases of the care and feeding of children. His presentation consists of the question and answer technic, which may not be easily read by some mothers. However, this technic is especially good for some of the sections, such as the chapters on behavior problems and contagious diseases, but it leads to complete stoppages of thought too frequently for effective study of the volume.

In asswering some of his questions on controversial subjects, Dr. Holt is rather dogmatic, as in the answers to the questions involved in the care of infants.

The chapters on "Artificial Feeding" seems to the reviewer to be much too elaborate for mothers. They, in all likelihood, would be confused by, and would not need such complete information on, the scientific reasons for different types of artificial formulas.

Dr. Holt's treatment of "Behavior Problems" is excellent, because it answers questions on definite psychiatric problems confronting many mothers and answers them simply and practically. He does not go into intricate academic discussions and uses no psychiatric terms which may be misunderstood by parents who are searching for clear knowledge.

"Common Ailments" is another section of the book that is well treated. The author gives the reader simple, accurate information which will help her to know how to handle illness situations intelligently.

This is probably as good a book in its field as there is for the pediatrician to suggest to the mothers who wish a book of this kind.

Whooping Cough. By Joseph H. Lapin, M.D. Price, $4.50. Pp. 237, with 40 illustrations. Springfield, Ill.: Charles C Thomas, Publisher, 1943.

This is the third book ever written on whooping cough; the last one, by Pospichill, of the Whooping Cough Hospital in Vienna, appeared in 1921. This is the first to be written in the English language. A total of 778 papers are abstracted, some in detail. The author states that "in the course of his own work on prophylaxis of well children, on the prophylaxis of 'contacts,' on the treatment of sick children and laboratory investigations, the ordeal of searching a literature growing ever more and more voluminous became so onerous that the creation of this book was conceived. Since all statistics agree that whooping cough is responsible for more deaths than any of the other contagious diseases of childhood, no one should be surprised at the resurgence of interest in it during the last ten years."

Although the volume presents adequate digests of the literature on most of the important phases of the problem of whooping cough, diagnosis, therapy, immunity and new control procedures receive most attention. This recently reawakened interest seems to be due, in the main, to procedures for immunization of nonexposed older infants.

Only relatively trivial discrepancies were found. Several of the seventeen chapters ("Hematology", "Roentgenology," "Treatment of Complications" and "Public Health Considerations"), consisting of but two to five pages each, might well have been included in other chapters; photomicrographs would have been better than some of the pen and ink sketches. Especially in the chapters on treatment there seems to be, at times, insufficient differentiation between measures of value and measures long since discarded because they were found worthless.

Dr. Lapin undertook a difficult task and has produced an outstanding contribution whereby further work in this field should be stimulated and facilitated. Pediatricians, health officers and all others interested in the eradication of whooping cough should profit greatly by a careful study of its pages. Especially in the postwar period it should prove valuable, because it will spare much time of students of pertussis throughout the world.

Children Can Help Themselves. By Marion Olive Lerrigo, Ph.D. Price, $2.25. Pp. 219, with no illustrations. New York: The Macmillan Company, 1943.

This book describes the growth and development of a boy from birth to the age of 12 years, with occasional mention of two playmates to help emphasize the differences in children. The author stresses the everyday problems, such as eating, sleeping, elimination, socialization, emotional control and cleanliness at each age, suggesting indirectly the proper attitude for parents to take toward these problems. The fact that this boy had security in well adjusted, intelligent parents is mentioned, but possibly this factor is not given sufficient credit for his success.

Although a description of the normal expectancy of behavior for each age is accurately given, the need for training is emphasized. The author is apparently worried over spoiling children, to the point of restricting emotional needs, especially in infancy. For example, she states: "They have agreed, not just yet at any rate (1 month), not to give him the pleasure of being rocked, sung to, patted and coaxed to go to sleep" and "She does not want to spoil David . . . she feels that there are ways of persuading him that he wants to sleep." Parents are left "on the fence" regarding thumb sucking by a quotation from a dentist to the effect that (at 2 years) "thumb guards are sometimes successful" and that "long continued thumb-sucking causes malformation of the mouth and teeth in some children while it seems to have no such effect on many others." Emphasis is placed on cleanliness, on cleaning of the finger nails, on picking up of toys and on manners. In this training the author seems to favor the norms for adult behavior rather than those for the various levels of growth and development, which are frequently mentioned and, for the most part, respected.

The book is well written, and the material is presented in an orderly, interesting manner.

Blood Groups and Transfusions. By Alexander S. Wiener, A.B., M.D. Third Edition. Price, $7.50. Pp. 438, with 69 illustrations and 106 tables. Springfield, Ill.: Charles C Thomas, Publisher, 1943.

This is the third edition of this excellent textbook. Two new chapters have been added. One dealing with the transfusion of stored blood and plasma should prove useful in its application to military medicine. The other describes the Rh factor and its role in erythroblastosis fetalis. In this chapter the subject is discussed in full and the laboratory methods utilized in the estimation of this factor are completely given. Dr. Wiener's writings are clear and lucid, and his exposition of the theoretic aspects of this subject and the descriptions of laboratory methods are excellent. From a practical standpoint it is unfortunate that under treatment it is so bluntly stated that "Rh negative blood of the same type as the infant's is the most

suitable choice." This is highly theoretic, as it is known that clinically any blood (except that of the mother) that is of the same type as that of the baby is life saving if given immediately. While the search for a donor with blood free of the Rh factor is going on, the life could be lost.

Almost all of the chapters have been revised and amplified by the addition of new material. This brings this excellent book entirely up to date and makes it a valuable asset to the library of every physician and hospital.

An Introduction to Group Therapy. By S. R. Slavson. Price, $2.00. Pp. 352, with no illustrations. New York: The Commonwealth Fund, 1943.

This book describes in detail a method of group psychotherapy employed at the Jewish Board of Guardians of New York since 1934.

The group in which a given problem child is to be placed is determined after careful social and psychiatric investigations. A well trained leader is in charge of each group. Materials for various types of activity are provided. Each individual child may carry on any aggressive or destructive activity he chooses. In addition, trips and outings are arranged and carried out by the group. Careful records are kept of the weekly meetings, and discussions are carried on with the group leaders.

The book describes the principles of group therapy, the nature of the records, the methods of choosing the clientele, the role of the group leader and the reactions of the individual problem children to the group. Many case illustrations, with "5 typical cases" described in detail, give a graphic picture of the whole procedure. The results are encouraging and indicate the value of this type of therapy if it is carried out by a trained personnel under psychiatric supervision.

La meningitis tuberculosa en el niño. By J. Bonaba, A. Carrau, C. Pelfort and B. Delgado Correa. Paper. Price, not given. Pp. 181, with 33 illustrations. Montevideo: J. Garcia Morales, 1943.

This is a complete and well written monograph in Spanish on tuberculous meningitis. The history, symptoms, pathology, diagnosis and frequency are amply discussed. The diagrams and photographs of the subjects and of the anatomic specimens and the roentgenograms are well chosen. Inasmuch as the authors give a clinical analysis of 1,000 observations on children, the reader feels that they know their subject well. The chapter on BCG vaccination is of especial interest. The authors are of the opinion that this form of immunization offers the only hope against this almost invariably fatal disease. The fact that there have been instances in which tuberculous meningitis developed in a vaccinated subject does not rule against this. In a series of 266 cases of tuberculous meningitis from 1929 to 1933 only 7 vaccinated patients died, while in 176 cases from 1934 to 1938 there were only 2 deaths among patients who had received the BCG vaccination. The bibliography is complete and contains references to publications in all of the principal languages.

The Mendoza Quadruplets. By Dr. Pastor Oropeza. Caracas, Venezuela: Editorial Elite, 1943. Pp. 40, no price given.

The author presents the story of the Mendoza quadruplets, who were born in the Venezuelan Andes. The birth weights were 1,980 Gm., 1,305 Gm., 1,375 Gm., and 1,235 Gm., respectively. They are living and well.

News and Comment

PERSONAL NEWS

New Appointment for Dr. Amos Christie.—Dr. Amos Christie, formerly of the American Red Cross in Washington, D. C., has recently been made professor of pediatrics at Vanderbilt University School of Medicine.

Directory of Pediatric Societies

INTERNATIONAL

International Association of Preventive Pediatrics

President: Prof S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

International Congress of Pediatrics

President: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
Secretary-Treasurer: Dr. Charles F. McKhann, University Hospital, Ann Arbor, Mich.

Canadian Committee:

Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto.
Secretary: Dr. H. P. Wright, 1509 Sherbrooke St. W., Montreal.
Place: Boston. Time: Postponed indefinitely.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

FOREIGN

Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

British Paediatric Association

President: Prof. L. G. Parsons, 58 Calthorpe Rd., Five Ways, Birmingham, England.
Secretary: Dr. Donald Paterson, 27 Devonshire Pl., London, W. 1.

Danish Pediatric Society

President: Dr. E. Lenstrup, Copenhagen.
Secretary: Dr. E. Gjørup, Dronning Louises Børnehospital, Copenhagen.

Nederlandische Vereeniging voor Kindergeneeskunde

President: Dr. J. H. G. Carstens, Servaasbolwerk 14ª, Utrecht.
Secretary: Dr. R. P. van de Kasteele, Laan van Poot 340,'s Gravenhage.
Place: Different places. Time: Three times a year.

Paediatrický Spolok na Slovensku

President: Dr. A. J. C. Chura, Lazaretská 11, Bratislava.
Secretary: Dr. P. Rados, Lazaretská 6, Bratislava.
Place: Pediatric Clinic, University Bratislava. Time: Six times a year.

Royal Society of Medicine, Section for the Study of Disease in Children

President: Dr. E. A. Cockayne, 98 Harley St., London, W. 1, England.
Secretary: Dr. R. Lightwood, 86 Brook St., London, W. 1, England.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:15 p. m.

Palestine Jewish Medical Association, Section of Physicians of Children's Diseases

President: Prof. S. Rosenbaum, 26 Bialkstr., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

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*Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

Sociedad Cubana de Pediatria

President: Dr. Angel A. Aballí Arellano, 17 No. 609 Vedado, Habana.
Secretary: Dr. Julio G. Cabrera Calderin, Hospital Mercedes L y 21 (Vedado), Box 2430, Habana.
Place: Cátedra de Clinica Infantil, Hospital Mercedes, Habana. Time: Last Wednesday of every month.

Sociedad Mexicana de Pediatria

President: Dr. Fernando López Clares, 12/a. Medellín 191, Mexico City.
Secretary: Dr. Jesus Gómez Pagola, Versalles 64, Mexico City.

Sociedad Venezolana de Puericultura y Pediatria

President: Dr. E. Santos Mendoza, Venezuela.
Secretary: Dr. P. Oropeza, Hospital de Niños, Caracas, Venezuela.

Société de Pédiatrie de Paris

President: Dr. B. Weill-Hallé, 49 Avenue Raymond Poincare, Paris, France.
Secretary: Dr. Jean Hallé, 10 bis Rue Pré aux Clercs, Paris, France.
Place: Hôpital des Enfants Malades, 49 Rue de Sèvres. Time: 4:30 p. m.
Place: Hôpital des Enfants Malades, 49 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

Uruguayan Society of Pediatrics

President: Dr. Nicolas Leone Bloise, Avenida Agraciada 2496, Montevideo.
Secretary: Dr. Héctor Mourigan, Avenida Agraciada 1464, Montevideo.

NATIONAL

American Medical Association, Scientific Assembly, Section on Pediatrics

Chairman: Dr. Hugh L. Dwyer, 315 Alameda Rd., Kansas City, Mo.
Secretary: Dr. Gilbert J. Levy, 188 S. Bellevue Blvd., Memphis, Tenn.

American Academy of Pediatrics

President: Dr. B. S. Veeder, 3720 Washington Blvd., St. Louis, Mo.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Region IV. Meeting cancelled.

American Hospital Association, Children's Hospital Section

Chairman: Dr. Joelle C. Hiebert, 299 Main St., Lewiston, Maine.
Secretary: Dr. W. Franklin Wood, McLean Hospital, Waverly, Mass.

American Pediatric Society

President: Dr. James L. Gamble, 300 Longwood Ave., Boston, Mass.
Secretary-Treasurer: Dr. Hugh McCulloch, 325 N. Euclid Ave., St. Louis.

Canadian Society for the Study of Diseases of Children

President: Dr. R. R. Struthers, 906 Drummond Medical Bldg., Montreal.
Secretary-Treasurer: Dr. Elizabeth Chant Robertson, Hospital for Sick Children, Toronto.

Society for Pediatric Research

President: Dr. Joseph A. Johnston, Henry Ford Hospital, Detroit.
Secretary: Dr. Mitchell I. Rubin, 1740 Bainbridge St., Philadelphia.

SECTIONAL

Intermountain Pediatric Society

President: Dr. Eugene Smith, 385-24th St., Ogden, Utah.
Secretary-Treasurer: Dr. W. C. Cheney, 837 Boston Bldg., Salt Lake City.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

NEW ENGLAND PEDIATRIC SOCIETY

President: Dr. Warren R. Sisson, 319 Longwood Ave., Boston.
Secretary-Treasurer: Dr. James Marvin Baty, 1101 Beacon St., Brookline, Mass.
Place: Boston Medical Library. Time: Four meetings a year, occurring from September to May.

NORTH PACIFIC PEDIATRIC SOCIETY

President: Dr. M. L. Bridgeman, 1020 S. W. Taylor St., Portland, Ore.
Secretary: Dr. C. G. Ashley, 833 S. W. 11th Ave., Portland, Ore.

ROCKY MOUNTAIN PEDIATRIC SOCIETY

President: Dr. G. R. Fisher, 23 E. Pikes Peak Ave., Colorado Springs, Colo.
Secretary: Dr. Joseph H. Lyday, 1850 Gilpin St., Denver.

SOUTHERN MEDICAL ASSOCIATION, SECTION OF PEDIATRICS

Chairman: Dr. William Weston Jr., 1428 Lady St., Columbia, S. C.
Secretary: Dr. Angus McBryde, 604 W. Chapel Hill St., Durham, N. C.
Place: Cincinnati, Ohio. Time: Nov. 16-18, 1943.

STATE

ALABAMA PEDIATRIC SOCIETY

President: Dr. Amos Gipson, 948 Forrest Ave., Gadsen.
Secretary-Treasurer: Dr. Ruth Berrey, 2021-6th Ave. N., Birmingham.

ARIZONA PEDIATRIC SOCIETY

President: Dr. Vivian Tappan, San Clemente, Tucson.
Secretary: Dr. Hilda Kroeger, Arizona State Health Dept. (Maternal and Child Welfare Division), Phoenix.

ARKANSAS STATE PEDIATRIC ASSOCIATION

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

CALIFORNIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. William C. Deamer, University of California Hospital, San Francisco.
Secretary: Dr. Charles W. Leach, 2000 Van Ness Ave., San Francisco.

FLORIDA STATE PEDIATRIC SOCIETY

President: Dr. Ludo Von Meysenbug, Box 3356, Daytona Beach.
Secretary: Dr. Robert Blessing, 409 Blount Bldg., Ft. Lauderdale.
Place: Concurrent with state association meeting at time of convention.

GEORGIA PEDIATRIC SOCIETY

President: Dr. T. F. Davenport, 104 Ponce de Leon Ave. N. E., Atlanta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.

HEZEKIAH BEARDSLEY PEDIATRIC CLUB OF CONNECTICUT

President: Dr. Edward T. Wakeman, 129 Whitney Ave., New Haven.
Secretary: Dr. Herman Yannet, Southbury Training School, Southbury.
Time: Three meetings a year.

ILLINOIS STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. Craig D. Butler, 715 Lake St., Oak Park.
Secretary: Dr. A. J. Fletcher, 139 N. Vermilion, Danville.

INDIANA STATE PEDIATRIC SOCIETY

President: Dr. K. T. Knode, 1105 E. Jefferson Bldg., South Bend.
Secretary-Treasurer: Dr. Mathew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

Iowa Pediatric Society

President: Dr. Mark L. Floyd, Children's Hospital, Iowa City.
Secretary-Treasurer: Dr. James Dunn, Davenport Bank Bldg., Davenport.

Medical Society of State of New York, Section on Pediatrics

Chairman: Dr. A. Clement Silverman, 608 E. Genesee St., Syracuse.
Secretary: Dr. Albert G. Davis, 307 Gas and Electric Bldg., Utica.

Medical Society of the State of Pennsylvania, Pediatric Section

Chairman: Dr. Elwood W. Stitzel, 403 Central Trust Bldg., Altoona, Pa.
Secretary: Dr. P. F. Lucchesi, Philadelphia Hospital, Philadelphia.

Michigan State Medical Society, Pediatric Section

Chairman: Dr. Charles F. McKhann, University Hospital, Ann Arbor.
Secretary: Dr. Mark F. Osterlin, Central Michigan Children's Clinic, Traverse City.

Mississippi State Pediatric Society

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

Nebraska Pediatric Society

President: Dr. E. W. Hancock, 820 Sharp Bldg., Lincoln.
Secretary-Treasurer: Dr. John M. Thomas, 1102 Medical Arts Bldg., Omaha.
Place: As announced by committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

New Hampshire Pediatric Society

President: Dr. MacLean J. Gill, 14 N. State St., Concord.
Secretary-Treasurer: Dr. Ursula G. Sanders, 46 Pleasant St., Concord.
Time: Twice yearly.

North Carolina Pediatric Society

President: Dr. Thomas M. Watson, Greenville.
Secretary: Dr. Frederick B. Haar, Greenville.

Oklahoma State Pediatric Society

President: Dr. Ben H. Nicholson, 301 N. W. 12th St., Oklahoma City.
Secretary: Dr. Luvern Hays, 108 W. 6th St., Tulsa.
Place: Oklahoma Club. Time: 6:30 p. m., fourth Friday of each alternate month from September to May, inclusive.

South Carolina Pediatric Society

President: Dr. Lonita Boggs, 301 E. Coffee St., Greenville.
Secretary-Treasurer: Dr. Hilla Sheriff, Wade Hampton Office Bldg., Columbia.

Texas Pediatric Society

President: Dr. F. H. Lancaster, 4409 Fannin St., Houston.
Secretary-Treasurer: Dr. John E. Ashby, 3610 Fairmount Ave., Dallas.

Virginia Pediatric Society

President: Dr. J. S. Weitzel, 3103 W. Franklin St., Richmond.
Secretary: Dr. Emily Gardner, 1100 W. Franklin St., Richmond.

West Virginia State Medical Society, Section on Pediatrics

President: Dr. Andrew Amick, 1021 Quarrier St., Charleston.
Secretary: Dr. A. A. Shawkey, Professional Bldg., Charleston.

LOCAL

Academy of Medicine of Cleveland, Pediatric Section

Chairman: Dr. J. D. Nourse, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. I. B. Silber, 10465 Carnegie Ave., Cleveland.
Place: Cleveland Medical Library Bldg. Time: October, December, February and April.

Academy of Medicine, Toronto, Section of Pediatrics

President: Dr. I. Nelles Silverthorne, 170 St. George St., Toronto, Canada.
Secretary: Dr. G. P. Hamblin, 2333 Bloor St. W., Toronto, Canada.

Bronx Pediatric Society

President: Dr. Forris E. Chick, 2325 University Ave., New York.
Secretary: Dr. Jacob H. Turner, 121 W. 197th St., New York.
Place: Concourse Plaza Hotel, 161st St. and Grand Concourse. Time: Every second Wednesday of each month, except June, July, August and September.

Brooklyn Academy of Pediatrics

President: Dr. Charles A. Weymuller, 85 Pierrepont St., Brooklyn.
Secretary: Dr. Lewis A. Koch, 62 Pierrepont St., Brooklyn.
Place: Granada Hotel. Time: Fourth Wednesday of October, November, February, March and April.

Buffalo Pediatric Society

President: Dr. A. Wilmot Jacobsen, 187 Bryant St., Buffalo, N. Y.
Secretary: Dr. Richard A. Downey, 786 Forest Ave., Buffalo, N. Y.
Place: Children's Hospital, 219 Bryant St. Time: 8:30 p. m., first Monday of each month from September to June.

Central New York Pediatric Club

President: Dr. Edward J. Wynkoop, 501 James St., Syracuse.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Places: Various cities in New York. Time: Third Tuesday of April and September.

Chicago Pediatric Society

President: Dr. Heyworth N. Sanford, 952 N. Michigan Ave., Chicago.
Secretary: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May, inclusive.

Cincinnati Pediatric Society

President: Dr. Lloyd K. Felter, 3144 Jefferson Ave., Cincinnati.
Secretary: Dr. T. Selkirk, 3530 Reading Rd., Cincinnati.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

Dallas Pediatric Society

President: Dr. John E. Ashby, 3610 Fairmount Ave., Dallas, Texas.
Secretary-Treasurer: Dr. Gladys J. Fashena, 4585 Belfort, Dallas, Texas.
Place: Bradford Baby Hospital. Time: 1 p. m., second and fourth Saturdays of each month.

Detroit Pediatric Society

President: Dr. Hugh Lewis, Detroit, Mich.
Secretary: Dr. John J. Pollack, 622-26 Maccabees Bldg., Detroit, Mich.
Place: Wayne County Medical Society. Time: 8:30 p. m., first Wednesday of each month from October to June, inclusive.

Fulton County Medical Society, Pediatrics Section (Atlanta, Ga.)

Chairman: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Secretary: Dr. Harry Lange, 478 Peachtree St., N. E., Atlanta.
Place: Academy of Medicine, 38 Prescott St. N. E. Time: Second Thursday of each month from October to April, 8 p. m.

Houston Pediatric Society

President: Dr. Raymond Cohen, 2300 Caroline St., Houston, Texas.
Secretary: Dr. Betty Moody, 526 Richmond Rd., Houston, Texas.
Place: College Inn, Houston. Time: Fourth Monday of each month.

Kansas City (Missouri) Pediatric Society

President: Dr. Edwin H. Schorer, 1103 Grand Ave., Kansas City.
Secretary: Dr. H. E. Petersen, Kirkpatrick Bldg., St. Joseph, Mo.
Place: Kansas City General Hospital. Time: On call.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Oscar Reiss, 2200 W. 3d St., Los Angeles.
Secretary-Treasurer: Dr. Elena Boder, 1830½ Lucille Ave., Los Angeles.
Place: Los Angeles County Medical Headquarters, 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

Medical Society of the County of Kings and the Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Harry Bikoff, 850 St. Marks Ave., Brooklyn.
Secretary: Dr. Henry Rascoff, 895 Eastern Parkway, Brooklyn.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m., fourth Monday of each month, October to April, inclusive.

Medical Society of the County of Queens, Inc., Section on Pediatrics

Chairman: Dr. Meyeron Coe, 217-02-91st Ave., Queens Village, N. Y.
Secretary-Treasurer: Dr. Edith A. Mittell, 144-38th Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. Harry A. Spigel, 2647 Connecticut Ave., Washington, D. C.
Secretary-Treasurer: Dr. Perry W. Gard, 2520 Woodley Rd., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N. W. Time: 8 p. m., fourth Thursday of every month.

Memphis Pediatric Society

President: Dr. F. T. Mitchell, 376 S. Bellevue Ave., Memphis, Tenn.
Secretary-Treasurer: Dr. Harry Jacobson, 1193 Madison Ave., Memphis, Tenn.
Place: John Gaston Hospital. Time: Quarterly.

Milwaukee Pediatric Society

President: Dr. John H. Reynolds, 1628 W. Wisconsin Ave., Milwaukee.
Secretary-Treasurer: Dr. F. J. Mellencamp, 324 E. Wisconsin Ave., Milwaukee.
Place: Milwaukee Athletic Club. Time: Second Wednesday of each alternate month, beginning with February.

New York Academy of Medicine, Section of Pediatrics

Chairman: Dr. Edith M. Lincoln, 600 Park Ave., New York.
Secretary: Dr. John D. Lyttle, Babies Hospital, New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Thursday of each month from October to May, inclusive, 8:30 p. m.

Northern California Affiliates

President: Dr. Crawford Bost, 490 Post St., San Francisco.
Secretary: Dr. William A. Reilly, 384 Post St., San Francisco.
Time: Second Thursday of September, November, January, March and May.

Northwestern Pediatric Society

President: Dr. Arild E. Hansen, University of Minnesota, Minneapolis.
Secretary-Treasurer: Dr. Albert V. Stoesser, 205 W. University Hospital, Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

Oklahoma City Pediatric Society

President: Dr. William M. Taylor, 1200 N. Walker St., Oklahoma City.
Secretary: Dr. G. R. Felts, 625 N. W. 10th St., Oklahoma City.
Place: Oklahoma Club. Time: Third Thursday of each month.

Philadelphia Pediatric Society

President: Dr. Theodore S. Wilder, Greene and Coulter Sts., Germantown, Philadelphia.
Secretary: Dr. Sherman Little, 1740 Bainbridge St., Philadelphia.
Place: College of Physicians, 19 S. 22d St. Time: Second Tuesday in March, May, October and December.

Pittsburgh Pediatric Society

President: Dr. Carl Ruder, 646 Washington Rd., Mount Lebanon, Pittsburgh.
Secretary-Treasurer: Dr. C. J. Stoecklein, 125 De Soto St., Pittsburgh.
Place: Pittsburgh Academy of Medicine. Time: Second Friday, alternate month from October to June, inclusive.

Richmond Pediatric Society

President: Dr. Stanley Meade, 913 Floyd Ave., Richmond, Va.
Secretary-Treasurer: Dr. Louise Galvin, 214 S. Boulevard, Richmond, Va.
Place: Richmond Academy of Medicine, 1200 E. Clay St. Time: 8 p. m., third Thursday of each month, except June, July and August.

Rochester Pediatric Society

President: Dr. Herbert Soule, 122 Rutgers St., Rochester, N. Y.
Secretary-Treasurer: Dr. Jerome Glaser, 300 S. Goodman St., Rochester, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee. Time: Third Friday of each month from October to May.

St. Louis Pediatric Society

President: Dr. Jerome Diamond, 508 N. Grand Ave., St. Louis.
Secretary-Treasurer: Dr. Mary A. McLoon, 408 Humboldt Bldg., St. Louis.
Place: St. Louis Medical Society Bldg. Time: First Friday of each month from November to June.

Seattle Pediatric Society

President: Dr. Frederick B. Joy, Stimson Bldg., Seattle.
Secretary: Dr. Sherod M. Billington, Medical Dental Bldg., Seattle.
Place: College Club. Time: Third Friday of each month from September to June at 6:30 p. m.

Southwestern Pediatric Society

President: Dr. Jeanette Harrison, 1136 W. 6th St., Los Angeles.
Secretary: Dr. Henry F. Gallagher, 1930 Wilshire Blvd., Los Angeles.
Place: Jonathan Club of Los Angeles. Time: First Wednesday in January, March May, September and November.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Campbell Harvey, 35 W. Huron St., Pontiac, Mich.
Secretary: Dr. Harry A. Towsley, University of Michigan, Department of Pediatrics and Communicable Diseases, Ann Arbor, Mich.

Westchester County Medical Society, Pediatrics Section (New York)

President: Dr. John B. Ahouse, 27 Ludlow St., Yonkers, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.
Place: Grasslands Hospital, Valhalla, N. Y. Time: Third Thursday in October, December, February and April.

THE AMERICAN JOURNAL OF DISEASES OF CHILDREN is published by the American Medical Association as a medium for the advancement of knowledge of the diseases of children and for the publication of scientific investigation in this field.

Manuscripts for publication, books for review and correspondence relating to the editorial management should be sent to Dr. Clifford G. Grulee, Chief Editor, 636 Church Street, Evanston, Ill., or to any other member of the Editorial Board. Communications regarding subscriptions, reprints, etc., should be addressed, AMERICAN JOURNAL OF DISEASES OF CHILDREN, American Medical Association, 535 North Dearborn Street, Chicago 10.

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Footnotes and bibliographies (the latter are used only in exhaustive reviews of the literature) should conform to the style of the *Quarterly Cumulative Index Medicus*. This requires, in the order given: name of author, title of article and name of periodical, with volume, page, month—day of month if the journal appears weekly—and year.

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Checks, money orders and drafts should be made payable to the American Medical Association.

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AMERICAN MEDICAL ASSOCIATION

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CONTENTS

PAGE

Late Effects of Lead Poisoning on Mental Development. Randolph K. Byers, M.D., and Elizabeth E. Lord, Ph.D., Boston 471

Radioactive Iodine Studies in Childhood Hypothyroidism. Joseph G. Hamilton, M.D.; Mayo H. Soley, M.D.; William A. Reilly, M.D., and Karl B. Eichorn, M.D., San Francisco 495

Regulation of Level of Vitamin A in Blood of Newborn Infants. J. M. Lewis, M.D., New York; Captain O. Bodansky, Medical Corps, Army of the United States, and L. M. Shapiro, M.D., New York 503

Effect of Maternal Rachitogenic Diet on Skeletal Development of Young Rat. Josef Warkany, M.D., Cincinnati 511

Case Reports:

Metabolism of Bone Salts in Resistant Rickets: Report of a Case, with Balance and Radioactive Tracer Studies. Lieutenant Commander Lewis Gunther (MC), U.S.N.R., and Elma T. Cohn, Ph.D.; Waldo E. Cohn, Ph.D., and David M. Greenberg, Ph.D., Berkeley, Calif. 517

Acute Glomerulonephritis Occurring in Three Children in the Same Family. Richard B. Tudor, M.D., New York 528

Chronic Hypergalactosemia. Floyd A. Norman, M.D., and Gladys J. Fashena, M.D., Dallas, Texas 531

Progress in Pediatrics:

Causes of Infantile Summer Diarrhea. Estenio Hormaeche, M.D.; Norris L. Surraco, M.D.; Cibo A. Pelufeo, M.D., and Pedro L. Aleffo, M.D., Montevideo, Uruguay 539

Abstracts from Current Literature 552

Book Reviews 569

News and Comment 580

Directory of Pediatric Societies 602